



**Medtronic**

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Rockville, MD 20850

RE: Petition for Reclassification of Totally Implanted Spinal Cord Stimulator for use in the Treatment of Chronic Intractable Pain

Dear Ms. Scudiero;

Two additional copies of our petition, dated January 31, 2000, are included in this package as requested by Dr. Bowsher. If you have any further requests regarding this matter please do not hesitate to contact Charles Swanson at (612) 514-3409 or myself at (612) 514-5198.

Sincerely,  
Medtronic Neurological and Spinal

Kathy Jo Fahey  
Sr. Product Regulation Manager

enclosure – 2 copies of “Petition for Reclassification of Totally Implanted Spinal Cord Stimulator for use in the Treatment of Chronic Intractable Pain”

00P-0788

*When Life Depends on Medical Technology*



**Medtronic**

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January 31, 2000

Center for Devices and Radiological Health (HFZ-410)  
Food and Drug Administration  
9200 Corporate Boulevard  
Rockville, MD 20850

Re: **Petition for Reclassification of Totally Implanted Spinal Cord Stimulator  
for use in the treatment of chronic intractable pain**

Dear Ms. Jan Scudiero:

On June 11, 1999, Advanced Neuromodulation Systems, Inc. (ANS) submitted a petition to the FDA requesting the reclassification of the "totally implanted spinal cord stimulator for pain relief" from Class III to Class II, (See *Attachment A, "ANS Petition"*, pages 2 and 25). Medtronic opposes this petition because the petitioner has not demonstrated that Class III controls are unnecessary to provide reasonable assurance of the safety and effectiveness of the device and that there is sufficient valid scientific evidence to demonstrate that Class II controls can provide a reasonable assurance of safety and effectiveness.

**I. Introduction**

ANS' petition is one-sided and fails to disclose significant data and information unfavorable to its position. For example, in its petition, ANS relied on what it characterized as "data maintained by FDA and the published literature" as support for its position, (*Attachment A, page 5*). In fact, the data presented in the petition pertains almost exclusively to one device, Medtronic's Itriel Spinal Cord Stimulator, and does not include either the Medical Device Reports ("MDRs") regarding devices that failed or, in particular, the troubling FDA history of the totally implanted spinal cord stimulator made by Neuromed, a company purchased by ANS. Specifically, on page 169 of the panel transcript, ANS states that in its MDR search, it "only included those IPG (Implantable Pulse Generator) systems which are currently in commercial distribution because they have had the longest duration, the longest time out in the market", (*Attachment B, "Panel Transcript"*, page 169). Conveniently excluded were those systems that either were removed from the market, i.e., the Cordis

product, or that didn't reach commercial distribution because the PMA review process identified safety and effectiveness issues, i.e., the Neuromed product. In the section entitled "Unfavorable representative data and information to the petitioner's position," petitioner neglects to mention not only the Neuromed history, which was clearly known to them, but other FDA actions and unfavorable MDRs (*Attachment A*, page 24). This omission is critical because it undermines petitioner's argument that Class II controls are sufficient to ensure the safety and effectiveness of the device. What is clear is that only Medtronic has successfully addressed the complex issues that define a safe and effective totally implanted spinal cord stimulator. We believe that the positive experience of only one manufacturer does not provide adequate assurance that Class III controls are not necessary to assure safety and effectiveness.

FDA failed to inform Panel of the legal standard for reclassification of a Class III implant because there was insufficient valid scientific evidence to define the generic type of device, the device's risks and performance parameters, and the controls necessary to ensure the safety and effectiveness of the generic type of device being considered for reclassification. In fact, FDA failed to correct the panel member representing industry whose misstatement of the legal standard (that the Panel should be looking at the least burdensome way to get products to market or the lowest classification that will provide reasonable safety and effectiveness). Instead of being required to overcome the presumption against down-classifying an implant and to determine if Class III controls were unnecessary to ensure reasonable safety and effectiveness, the Panel was given a lower standard. The Panel was lead to believe that its obligation was to seek the lowest reasonable class.

Inclusion of information and data on only one device also causes an additional problem. As is discussed below, under section 520(c) of the Food, Drug, and Cosmetic Act ("Act"), confidential commercial and financial information, and trade secret data, such as methods of manufacture and product composition, cannot be used by FDA in reclassifying a Class III device. Thus, Medtronic's PMA data are prohibited from being used by the Agency to approve, classify, or reclassify devices. If the Agency reclassifies the generic type of device to Class II, it will have to use Medtronic's PMA data to determine substantial equivalence for at least the first 510(k) submitted for a totally implantable spinal cord stimulator. Without Medtronic's proprietary data, we believe there is not adequate valid scientific information on which to base a reclassification.

Omissions by FDA at the panel meeting include that, in its presentation, FDA discusses the history of IPG systems and only focuses on RF systems, which are Class II devices that present different risks and benefits from IPGs. FDA failed to discuss the 1995 letter from Dr. Susan Alpert to Medtronic (Bob Klepinski) in which Dr. Alpert emphasizes PMA Class III IPG system controls are necessary because of their significant technological differences from a Class II RF system (See *Attachment C*, Dr. Alpert's letter). We see nothing in the petition or in the Panel's consideration which refutes the Agency's position as espoused in Dr. Alpert's letter.

Accordingly, we request that FDA deny the petition and keep the device within a Class III designation, on the grounds that: (1) petitioner has not demonstrated that Class III controls are unnecessary to provide reasonable assurance of the safety and effectiveness of the device; (2) there is insufficient valid scientific evidence to demonstrate that Class II controls can provide a reasonable assurance of safety and effectiveness; (3) due to the irregularities in the proceedings the Panel was misinformed; (4) a breach of confidentiality entitled to Medtronic would occur if our PMA data was used improperly; and (5) FDA has ruled as recently as 1995 that the totally implantable spinal cord stimulator is a Class III device.

**II. ANS Has Not Overcome the Presumption against Reclassification of a Class III Implant**

Under the Act, a post-amendment device (*i.e.*, a device not introduced or delivered for introduction into commerce for commercial distribution before the date of enactment of "The Medical Device Amendments of 1976") is automatically classified into Class III under section 513(f)(1) if it is found to be not substantially equivalent to a predicate device. However, under section 513(f)(3)(A) of the Act, FDA may initiate reclassification for such a device or, as here, a manufacturer may petition FDA for reclassification of the device into Class I or Class II. Significantly, for implants such as the device at issue, there is a presumption against reclassification. FDA must deny a petition for reclassification of an implant unless it determines that classification in Class III is not necessary to provide reasonable assurance of safety and effectiveness of the device, [§513(3)(B)(i) and (C)(i)]. Indeed, the regulations are very clear that for implants, not only the Panel but also the Agency must have valid scientific evidence ("data satisfying the requirements of §860.7") to rebut the presumption, [21 CFR §860.93 (a) and (b)].

In order to recommend reclassifying a Class III device that is an implant, the Panel must find that classification in Class III is unnecessary to provide reasonable assurance of safety and effectiveness of the device.<sup>1</sup> Similarly, to order reclassification, FDA must determine that classification in Class III is unnecessary to provide reasonable assurance of safety and effectiveness of the device [§513 c (f)(3)(B)(i) and (C)(i)] and must have data acceptable as valid scientific evidence under 21 CFR §860.7(c)(2) to support a change in classification [21 CFR §860.93(b), 21 CFR §860.134(b)(6)]. Indeed, if the Agency proposes to reclassify a Class III implant, the Commissioner must provide:

“... a full statement of the reasons for [reclassifying the device]. A statement of the reasons for not classifying or retaining the device in Class III may be in the form of concurrence with the reasons for the recommendation of the classification panel, together with supporting documentation and data satisfying the requirements of §860.7 and an identification of the risks to health, if any, presented by the device,” [21 CFR §860.93(b)].

In other words, FDA must justify with great particularity its basis and reasons for reclassifying a Class III implant.

If FDA determines that a petition for reclassification does not contain any deficiencies that would preclude a decision, FDA may for good cause shown refer the petition to the appropriate classification panel for review and recommendation on whether to approve or deny the petition, [21 CFR §860.134(b)(3)]. In order not to be deficient, a petition for reclassification must contain, among other things: a specification of the type of device for which reclassification is requested; a full statement of reasons why the device should be reclassified, including how the proposed classification will provide a reasonable assurance of safety and effectiveness and supporting data meeting the criteria set forth at 21 CFR §860.7, [see 21 CFR §860.123(a)(6)], and representative data and information known by the petitioner that are unfavorable to the petitioner's request, [21 CFR §860.123(a)(7)]. Importantly for implants, the information in support of a reclassification petition must overcome the presumption against reclassifying such devices out of Class III.

<sup>1</sup>The Panel's recommendation must include “(1) a summary of the reasons for the recommendation; (2) a summary of the data upon which the recommendation is based, accompanied by references to the sources containing such data; (3) an identification of risks to health (if any) presented by the device; . . . (6) in the case of a recommendation for classification of an implant . . . into . . . class II, a statement of why premarket approval is not necessary to provide reasonable assurance of safety and effectiveness of the device, accompanied by references to supporting documentation and data satisfying the requirements of §860.7, and an identification of risks to health, if any, presented by the device,” [21 CFR §860.84 (d)].

Valid scientific evidence is defined by FDA to include evidence from: well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use [21 CFR §860.7(c)(2)]. "The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use," [*Id.*; see also *Ethicon*, 762 F.Supp. 382, 387 (D.D.C. 1991)]. However, the Agency cannot consider "isolated case reports, random experience, reports lacking in sufficient detail to permit scientific evaluation, and unsubstantiated opinions" to support a reclassification [See 21 CFR §860.7(c)(2)<sup>2</sup>]. It is important to note that valid scientific evidence used for reclassification must be publicly available, or otherwise legally available to the petitioner [§520(c), 520(h)(4)].

Importantly, a petition for the reclassification of a device will be considered a petition for the reclassification of all substantially equivalent devices within that generic type [21 CFR §860.120(b)]. Thus, a meaningful specification of the type of device proposed for reclassification is critical to a regulatory decision. A generic type of device is defined as a grouping of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness; and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness [21 CFR §860.3(i)]. "The Agency's characterization of a generic class or type of device is fact-specific," [*Ethicon, Inc. v. Food and Drug Admin.*, 762 F.Supp. at 387].

<sup>2</sup> As part of the safety showing, the valid scientific evidence must "adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use," [21 CFR §860.7(d)(1)]. A demonstration of effectiveness requires valid scientific evidence showing "in a significant portion of the target population that use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, will provide clinically significant results," [§860.7(e)(1)]. Valid scientific evidence demonstrating effectiveness principally must consist of well-controlled clinical studies unless FDA authorizes reliance on other types of valid scientific evidence, which it may do where such a requirement is not reasonably applicable to the device in question [§860.7(e)(2)]. For purposes of reclassification such evidence must define risks and performance parameters and demonstrate the controls that could provide a reasonable assurance of safety and effectiveness.

In considering whether or not a Class III designation is unnecessary to provide a reasonable assurance of safety and effectiveness, "the question is whether the administrative record contains sufficient information for the Agency to understand the device and sufficient evidence to demonstrate that factors determining the device's safety and effectiveness are controllable," [*Ethicon*, 762 F.Supp at 388]. Valid scientific evidence must address the following factors that a panel and FDA must consider in understanding the device and determining its safety and effectiveness for purposes of reclassification: "(1) the persons for whose use the device is represented or intended; (2) the conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use; (3) the probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and (4) the reliability of the device," [21 CFR §860.7(b)]. In addition, "valid scientific evidence in the record [must] correlate the control of performance parameters to safe and effective use of the device," [*Ethicon*, *supra* (citing 21 CFR §860.7(c) and §860.5(f)]. Thus, petitions lacking adequate valid scientific evidence to characterize the generic type or device, identify device risks and performance parameters, and describe methods of controlling each risk and ensuring each performance parameter are deficient because without such evidence the Agency cannot legally reclassify a device.

ANS' petition is deficient on its face and should not have been referred for Panel consideration because it did not provide adequate valid scientific evidence for FDA to make a reclassification decision and failed to disclose material information known to both ANS and FDA that is adverse to its reclassification request. Nonetheless, FDA referred the petition to a Panel which recommended reclassification into Class II. FDA must reject the Panel's recommendation and deny the reclassification petition because, in addition to procedural irregularities in the Panel process that we describe below, ANS has fallen far short of meeting the legal standard for reclassification, including valid scientific evidence defining IPG risks, performance parameters and controls.

### **III. The Administrative Record Establishes That ANS Has Not Met The Legal Standard For Reclassification**

The administrative record establishes that ANS has failed to meet the legal standard for reclassification. It is clear from the petition and the panel meeting that the device is inadequately characterized and that there is insufficient information from which to determine the device's performance parameters, all of the risks presented by the device, and the special controls adequate to address those performance parameters and risks. Moreover, the special controls recommended by the Panel are inadequate to provide a reasonable assurance of safety and effectiveness.

For example, ANS failed to point out all risks associated with a battery failure. A battery that leaks after implant would affect the patient significantly. ANS has proposed additional labeling to address the multiple battery risks such as leaking and end of life that were identified in the petition. ANS also recommends that special controls include the European Standard for Active Implantable Devices. Although the Panel accepted these ANS recommendations, neither special control would aid in decreasing occurrence of battery leakage or other failure modes of the device. And neither can replace the Class III, pre-PMA inspection in alerting the FDA to serious manufacturing problems.

**A. Factual Background**

The device for which reclassification is requested is inadequately characterized in terms of indications for use and manufacturing process. This information is critical to define a generic type of device and to understand the risks it presents.

Everyone, including ANS and FDA, acknowledged the incomplete nature of the IPG MDRs and the limitations on using the information. Nevertheless, MDRs are the major item discussed at the panel meeting as the basis upon which the special controls are proposed. The MDR presentation by ANS in both the petition and at the panel meeting is skewed to eliminate at least one significant risk for which there is no special control. In addition, ANS only uses MDRs generated by the devices currently on the market, which also skews the presentation of risks. Although the literature is also used as purported valid scientific evidence supporting reclassification, ANS inaccurately portrays the articles.

**1. Petition Deficiencies**

ANS' petition has a number of failings that seriously undermine its position regarding reclassification. These include conflicting indications for use, an absence of manufacturing information, an inaccurate portrayal of the literature, and deficient special controls.

In addition, in its petition, ANS omitted known information on the safety hazards of the Neuromed and Cordis devices. This omission was continued in its description of the history of the IPG system at the panel meeting, where ANS did not report the failure of the Neuromed and Cordis devices to make it to market and the reasons therefore, (*Attachment B*, page 157). Accordingly, not all significant performance parameters and risks of the device were presented and discussed in the reclassification process.

a. Indications for Use

The FDA is fully aware of the difference in review and approval level of labeling between a Class III and Class II device. The FDA labeling review is critical. The FDA has labeling authority for Class III PMA devices. The FDA does review labeling for 510(k) devices but does not have the same degree of preapproval authority and exercises control primarily on a postmarketing basis. Since it is a critical difference, it is prudent to review the deficiencies noted in the ANS' petition and panel presentation.

A device is composed of its technology and its indications for use. Medtronic's approved labeling for its SCS (spinal cord stimulator) provides that the indication for use of the SCS Class III device is to "aid in the management of chronic intractable pain of the trunk or limbs." In other words, the Class III approved device appears to differ from the device ANS is trying to reclassify. ANS' device is defined by indications for use that are unapproved and reclassification is an improper means to obtain approved labeling claims.

First, ANS' petition statements regarding the device's indications for use, which ANS later changed at the panel meeting, result in an inadequate characterization of the device. In the petition, ANS stated that it was requesting reclassification of the "totally implanted spinal cord stimulator for pain relief from Class III to II," (*Attachment A*, page 1). Later in the petition, ANS described the indications for use of the device as "treating a variety of chronic pain conditions. These include tumors, brachial plexus injuries, cord injury, phantom limb pain, reflex sympathetic dystrophy, ischemic limb pain, multiple sclerosis, peripheral vascular disease (sic) arachnoiditis, and pain after failed spine surgery," (*Attachment A*, page 5). In addition, the petition states that "a recent report of the results of a series on failed back surgery syndrome and neuropathic pain of peripheral origin has shown good long-term outcome in 50-60% of cases treated...Pain syndromes associated with peripheral neuropathy ...reflex sympathetic dystrophy (or complex regional pain syndrome 1)...complex regional pain syndromes... also been found to be highly effective in treating the pain from angina and peripheral vascular disease...coronary artery bypass surgery," (*Attachment A*, page 8). The petition also mentions use for "patients with chronic low back and lower extremity pain following prior surgery (failed back surgery syndrome)," (*Attachment A*, pages 10-11), and for "peripheral neuropathy," (*Attachment A*, page 19). However, at the panel meeting ANS described the indications as follows:

"Our reclassification petition is not to reclassify this device outside the current classification for RF systems, which is spinal cord stimulation for the indication of the treatment of chronic pain of the trunk and limb -- trunk and/or limbs, either as a sole mitigation agent or as an adjunct to other modes of therapy used in a multidisciplinary approach," (*Attachment B*, page 159).

On page 165, Dr. Baralot, presenting to the Panel for ANS, states

"What are the indications for spinal cord stimulation? I would say that the indications are shared between the two types of systems. Chronic pain makes up for the bulk of it, and the different subcategories of chronic pain - - RSD, causalgia - - they are part of the complex regional pain syndromes. And then different pains - - neuropathy, brachiolexis, nerve root avulsion, failed back surgery - - as you know, that probably makes up for more than half of the implants today in the United States - - neuralgias, arachnoiditis, and then pain due to peripheral vascular disease, and pain due to angina, which are two relatively more recent applications," (*Attachment B*, page 165).

In conclusion, ANS, confused the record significantly in describing the indication for use and the Panel appeared to recommend the indication which is different from those FDA approved indications within Medtronic's PMA.

To further illustrate the significance of the distinction between a Class III and a Class II device, Dr. Richard North, the Medtronic representative at Panel, points out,

"...after market release the FDA has no control over medical practice, and a physician can use a device for any indication, anatomical site, or treatment option. In my opinion this is the [sic] another significant risk the FDA is taking in the manner: granting Class II to an active implantable device that may be used in any number of ways 'off label'," (*Attachment D*, Dr. North's letter).

Because of the confusion introduced by ANS in their petition, and carried through the Panel proceedings, and because of concern regarding "off label" use, reclassification is inappropriate.

b. Manufacturing

Also contributing to the device's inadequate characterization is ANS' failure to include any manufacturing information in its petition. Manufacturing processes are critical to the device's character as well as to an understanding of the risks it presents. In the Ethicon case, manufacturing information was presented and cited by the court, indicating its significance, [Ethicon, Inc. v. Food and Drug Admin., 762 F.Supp. 382 (D.D.C. 1991)]. Specifically, "a substantial body of patient literature and journal articles have been published that completely describe the necessary processes for manufacture," [Id. at 389]. While the party opposing reclassification in that case argued that more detailed manufacturing information was necessary in order to "adequately understand the manufacturing variables and conditions that may affect the safety and effectiveness of the particular device," the court found that the manufacturing information presented along with the studies and reports in the record was sufficient to show that the device's "performance parameters and uses are well-understood" and that "variability of composition and performance is minimal," [Ethicon, 762 F.Supp. at 387, 388]. Unlike that case, ANS has presented nothing regarding the manufacturing process, and such information is critical to understanding not only the character and characterization of the IPG device, but the performance parameters that can only be controlled by the PMA process.

Furthermore, ANS' comment - the only risk unique to IPGs is the greater difficulty of turning off runaway stimulation and that there have not been a large number of these reports - is incomplete. A comprehensive risk analysis of IPGs will identify multiple risks that need to be addressed before reclassification can reasonably be considered. Although many of these risks are similar to RF devices, the overall risk is greater with IPGs due to the internal power source. With a RF device, a circuit failure that results in inappropriate stimulation can be quickly and easily returned to a safe mode by simply turning off the external transmitter, unplugging the antenna, or removing the antenna.

Some of these risks can be managed through suitable industry standards. However, this does not always guarantee safety even for the particular risk addressed by a standard. An example is Net DC current. The ANSI/AAMI NS14 Standard calls for a Net DC current through the stimulating electrodes not to exceed 10 microamps DC. If tested as shown in the standard it is easy to demonstrate net DC less than 10 microamps under steady state conditions. However, with newer RF or IPG neurostimulators, the control of Net DC becomes more difficult with the multitude of parameters that can be varied dynamically in time, specifically in situations where individual electrodes are shared between two automatically alternating stimulation programs. Examples include on/off cycling, softstart/softstop, multiple channels, etc. Even the standard engineering method of using individual coupling capacitors in each output electrode of the IPG does not guarantee an acceptable Net DC when common electrodes are shared between channels.

Another example of risk is the use of custom designed integrated circuits or ASICs (application specific integrated circuits), instead of commercially available "off-the-shelf" integrated circuits. ASICs are required for modern neurostimulator devices, both RF and IPG, where complexity and size constraints dictate. The design of ASICs requires a high degree of design skill and manufacturing process control. One area of concern is manufacturing test. Each integrated circuit needs to be tested at the time of manufacture to assure no defective circuits are inadvertently released for use in implantable product. If defective circuits are released for use in implantable product, the result can range from insignificant to serious (e.g. inability to turn on/off stimulation, over stimulation, and loss of muscular control or battery heating) depending on the nature of the defect. With a RF powered stimulator, you simply remove or disconnect the antenna or turn off the transmitter. With an IPG, a control failure can result in a trip to the hospital for an emergency explant of the IPG. If a heavy load is placed on the battery due to an integrated circuit failure, the battery can heat up significantly potentially causing severe pain or tissue necrosis.

To summarize, modern neurostimulators are complex devices. The risks associated with this complexity are greater than with RF powered stimulators.

Manufacturing is a critical issue. Both Neuromed and Cordis attempted and failed to master the manufacturing intricacies of the device necessary to make an IPG device safe and effective for the intended use. This product type is so complex that design problems or manufacturing control problems in the devices manufactured by Cordis and Neuromed were not detected until late in the PMA review process (Neuromed) and after approval of the PMA (Cordis). Neuromed's IDE was approved and the clinical study -- a controlled, prospective, randomized trial -- was underway before critical problems were identified. During the pre-PMA inspection (part of Class III controls) of Neuromed's facility, gross under reporting of MDRs and unanticipated adverse events within the clinical study were uncovered. This discovery

resulted in a decision not to proceed with the PMA approval process. Cordis attempted to design and manufacture an implanted device with internal battery. This device was removed from the market after PMA approval because issues relating to the battery and its technology resulted in patient harm. This battery's electrolytes diffused through its silicone holder, i.e., the electrolytes leaked within the implanted device. This leakage caused the control circuit to fail, which in turn caused the device to either (a) not be programmable (not able to turn off the device), (b) change parameters on its own, or (c) cease functioning. At a minimum all of the failures resulted in device explant, and some in patient harm.

These examples reinforce the need for the highest bar to ensure patient safety and effectiveness of the device. Detailed and specific PMA controls prevented the commercial approval of these devices. We question whether 510(k) controls would have identified these problems before the devices were on the market, greatly and unnecessarily increasing the patient risk.

Several Panel members expressed their discomfort with the lack of manufacturing information presented by ANS and FDA. Yet Panel members favored reclassification without a full understanding of so-called special controls and without critical information. For example, Panel member Dr. Ku stated that he did not think there was

"...data that would make it possible to easily and reliable [sic] to produce a component that would have a low failure rate. If that can be done, as Dr. Walker suggests, relatively easily, then I think it [reclassification] is quite reasonable because it is just an engineering issue. And if you can with regular manufacturing controls, assure that the failure rate of this product is going to be low, then I don't have a problem with that. But on the available data that is presented in the petition itself, I don't have that evidence," (*Attachment B*, page 238<sup>3</sup>).

He nevertheless decides in favor of reclassification but reiterates his disappointment that petitioner did not present "data to show that it is easy or reliably possible through standard manufacturing to achieve these conditions of reliability," (*Attachment B*, page 241). Of course, there is no such data or information to satisfy Dr. Ku's concerns. Only Medtronic in its PMA has demonstrated appropriate

<sup>3</sup> 1st concern is the design of the circuitry; also that it is designed not to fail or has been tested adequately so that all the bugs have been worked out [and] whether or not the programming has been tested, seems to be the main question, (*Attachment B*, page 229). He also asks whether or not it is very difficult to design a system that is relatively fail safe, or it just takes a bunch of smart engineers to work real hard to do it, (*Attachment B*, page 229).

product design and manufacturing controls that resulted in a clinically safe and effective device. However, FDA may not use this confidential commercial information because the federal regulations prohibit the use of PMA data [See §520(c)].

Control of an active implantable device is a very complex task. In fact, there are no special controls specific to the manufacturing and testing of IPGs. Although ANS proposes use of European standards as special controls, ANS failed to show with valid scientific evidence that these controls will provide reasonable assurance of safety and effectiveness. It is important to note that there is an overall European Standard for Active Implantable Devices and a specific standard for pacemakers, but there is no standard, as yet, for neurostimulators. Even if it did exist, the standard would not cover all aspects of safety and effectiveness and by itself serve as an adequate alternative to PMA controls.

The Panel member who apparently convinced Dr. Ku of the simplicity of manufacturing a safe and effective IPG device, Dr. Walker, made unfounded assumptions. Dr. Walker states that he is not concerned about whether or not it is theoretically possible to make a safe device and says "it would be left to design controls that would be imposed on ANS to be sure that they achieved the same high degree of reliability that other people in this business have achieved," (*Attachment B*, page 230). Just because Medtronic has done it does not mean that "good engineers who work real hard" (assuming all manufacturers have such engineers) can do it, (*Attachment B*, page 229). Moreover, design controls are not the answer. The Cordis' and Neuromed's devices undoubtedly used some form of design controls. They still failed after they were implanted in humans. Dr. Walker understated what it takes to design and build a safe and effective IPG. Design controls without adequate FDA oversight provided by the PMA process are simply not enough to assure that this device is safe and effective for clinical use.

Dr. Ku also confused Panel members with a seemingly unsubstantiated statement. Specifically, "You can bench top test this thing and achieve a reliability of .03 % failure rate for 100 different devices, then implanting it, the technology is known," (*Attachment B*, page 271). It is not clear where the .03% bench failure rate came from. It is not present in the petition, the materials provided to the Panel members nor the Medtronic PMA. Moreover, the statement is potentially grossly misleading as to the clinical safety and effectiveness of the device. If the technology was that simple then why have two companies failed to bring an implantable device to market especially when one of the companies had extensive experience with implantable devices (Cordis with its pacemakers) and the other had years of experience in partially implantable SCS systems (Neuromed with its RF devices).

Further, it is well understood that bench testing does not conclusively predict operation of a device in a biological system. Dr. Edmondson recognized this in during the Panel discussion, stating:

"I would like to make another push for a clinical study before release. There are many nuances that you can test in the laboratory to determine frequency, output, all of these engineering issues. But when you implant a device and somebody goes out and mows their lawn and a number of other things, there may be some nuances intrinsic to that device. So I think that a limited study that focuses questions is really warranted," (*Attachment B*, page 272).

Almost all of the Panel members were concerned with Medtronic's statement that manufacturers were inspected every five years instead of the statutory two, indicating their belief that control of manufacturing of these devices is important. As a special control, the Panel recommended inspections "at level III." This was intended to mean inspections every two years. The Panel discussed premarket inspection and seems to have been convinced by (1) FDA's representative, who stated that there is no real difference between what is done at a premarket inspection and what is done at the biennial inspection and (2) the Chair stating that premarket inspection would not address battery failure, which is the main concern, (*Attachment B*, pages 274 - 277), and did not recommend premarket inspection as a special control. The Panel member who requested it be a special control dropped the request, (*Attachment B*, pages 274 - 277). However, the final vote is phrased in terms of "inspection at level III", giving the impression that the Panelists thought the biennial inspections that they agreed to were tantamount to the inspections applicable exclusively to Class III devices, (*Attachment B*, page 278).

c. Mischaracterization of the Scientific Literature

ANS mischaracterized the scientific literature in its petition. This would lead the Panel to draw inaccurate conclusions from the medical community.

ANS at least once misquoted the scientific literature in the Turner article on page 14 of its petition. ANS portrayed this article as demonstrating multiple studies with large numbers of patients being satisfactorily treated with spinal cord stimulation using both RF and IPG systems. In his article Dr. Turner's point is that pre-1995 clinical studies were probably not carried out under Good Clinical Practices (GCP) and fail to either quantitatively or qualitatively review the enrolled patient population to draw effective conclusions. This removes approximately twenty of the articles that ANS relies upon to support its view that the device is well understood and easily controlled.

Further mischaracterizing the data, ANS expert, Dr. Baralot states that the literature does not specify whether the systems were RF or IPG, (*Attachment B*, page 163). This is simply not the case; we were able to define in most cases which system was referenced in the medical/scientific literature.

There is insufficient valid scientific evidence to identify each performance parameter and risk posed by the device and to identify methods to control each. The evidence in the administrative record consists mainly of literature reports on Medtronic's device. This only provides a limited picture of one device that has been successfully manufactured for approximately 15 years. To extrapolate the same conclusions to devices introduced on the market today under a Class II scenario would be an error. Also of importance, the failed efforts of two other companies are not reflected in this literature summary. In other words ANS provided FDA and the Panel a confused and inaccurate picture of the information available about IPG devices.

Furthermore, all clinical research reported in the scientific literature for the implantable stimulator is based on Medtronic devices only. ANS suggested that its implantable device currently in design would have the same successful results as the Medtronic devices; however, this is speculative and not valid scientific evidence and therefore cannot support the reclassification of IPGs.

d. Alterations of transcript

Based on a comparison of the transcript to the audiotape, we have identified a number of alterations of the transcript that we believe specifically affect the meaning of the proceedings. For example, in the midst of Dr. Gonzales' statement that the 25 percent "Other category" for MDRs is problematic, the transcript omits the statement "I'd like more information," (*Attachment B*, page 233). On page 261, the transcript shows that Dr. Gonzales asked Dr. Walker whether there are standards on "other aspects of failure such as leakage, toxicity," (*Attachment B*, page 261). In fact, Dr. Gonzales asked Dr. Walker whether there are any standards on "other aspects of failure such as leakage, toxicity, other problems." This limitation in the transcript alters Dr. Walker's response from not being aware of standards related to leakage, toxicity and other failure modes to not being aware of standards just related to leakage and toxicity.<sup>4</sup>

e. Omissions at Panel

FDA failed to include within its presentation reference to the 1995 letter from Dr. Susan Alpert to Medtronic (Bob Klepinski) (*Attachment C*), in which Dr. Alpert states,

<sup>4</sup> Hearings-On-The-Line ®, National Narrowest Network, LP, P.O. Box 9597, Friendship Station, Washington, DC, 20008

"FDA determined that this Medtronic device was not substantially equivalent to devices classified in 21 CFR §882.5880 based on significant technological differences. For example, the Medtronic device employs an implanted device containing a power source; whereas, the devices classified in 21 CFR 882.5880 employs an implanted device comprised entirely of passive components with necessary energy being provided by an external device," (*Attachment C*, Dr Alpert's Letter).

Furthermore Dr. Alpert states,

"We believe this unequivocally establishes that Medtronic Totally Implantable Spinal Cord System is by statute a Class III device for which an approved PMA is required for marketing," (*Attachment C*, Dr. Alpert's Letter).

Importantly, FDA states that there are "significant technological differences" between an IPG and a RF system, and that "this unequivocally establishes" the Medtronic IPG as a Class III device. Nothing has occurred since 1995 to our knowledge which would change this opinion of FDA's then Director of the Office of Device Evaluation.

**B. Under the Facts and Law, FDA Must Deny ANS' Reclassification Petition**

**1. Lack of Adequate Valid Scientific Evidence in the Administrative Record**

The administrative record described above demonstrates that reclassification is inappropriate for many reasons. First, it is inappropriate because the IPG is not a well-characterized generic type of device. The indications for use that the Panel considered are poorly defined and ANS provided conflicting information in its petition and at Panel regarding the device's use. Moreover, no manufacturing information was provided to FDA or the Panel regarding this complex device, resulting in an inadequate characterization of the IPG. What is clear is that manufacturing is a key element in producing a safe and effective IPG.

Second, there is insufficient valid scientific evidence to identify each performance parameter and risk posed by the device and to identify methods to control each. The evidence in the administrative record consists mainly of literature reports on Medtronic's device. This information only provides a limited picture of one device that has been successfully manufactured for approximately 15 years. To extrapolate the information to devices that do not exist and for which there is no valid scientific evidence as a basis for reclassification would be an error. Two out of three companies

have failed to market an IPG for spinal cord stimulation. The actual device experience in this field is drastically different from the way it is described in the petition.

The MDR data is incomplete because it does not include reports from devices other than Medtronic, and therefore eliminates mention of the risk of battery leakage and skews the significance of the other risks. Further, there was no MDR denominator information; the lead reviewer at FDA, Dr. Bowsher, stressed in her introduction that while the MDR data could give the Panel a "feel" for the type of risks, it could not be used to calculate the rates of actual events. FDA's presentation was also deficient in that it discussed the history of RF systems but not IPG systems, and failed to discuss Dr. Susan Alpert's 1995 letter stating that the IPG system is significantly technologically different from the RF systems, thus requiring Class III PMA status. Moreover, there were a number of misleading and incorrect statements made by panel members and others during the presentations and deliberations, such as Dr. Edmondson's gross understatement of the consequences of problems with an implanted pulse generator, (*See Attachment B*, page 224). If an implanted pulse generator is not working, whether due to uncontrolled stimulation or a failed or leaking battery, the device must be explanted with all the attendant risks of surgery and anesthesia. Such misstatements regarding critical risk and performance parameters may have, and in some cases appear to have, influenced panel members. Clearly, the administrative record is too narrow and unreliable to provide a basis for determining that Class III controls are unnecessary to ensure the reasonable safety and effectiveness of the device.

**2. FDA is Prohibited from Using Medtronic's PMA Data**

Importantly, FDA may not use Medtronic's PMA data to overcome the deficiencies of the petition. No data from PMAs approved prior to the effective date of the Food and Drug Modernization Act of 1997 (FDAMA) may be used by FDA for any purpose, including reclassification or a determination of substantial equivalence [See section 216 of FDAMA, codified at §520 (h)(4)] providing that any information contained in a PMA, excluding trade secrets, "shall be available, 6 years after the application has been approved for use by the Secretary in approving another device, determining whether a PDP has been completed for another device, establishing a performance standard or special control, or classifying or reclassifying another device." Use of data from PMAs such as Medtronic's that were approved before the effective date of FDAMA is an illegal retroactive application of section 216 and thus prohibited, [See *Landgraf v. USI Film Products*, 114 S. Ct. 1483, 1497 (1994)]; the presumption against retroactive legislation is deeply rooted in the law.

To overcome the presumption against retroactive application of the law, a "clear statement" from Congress of its intent that the law be retroactively applied is required [See Lindh v. Murphy, 117 S. Ct. 2059, 2062 (1997) (citing Landgraf)]. There is no legislative history on section 216 to suggest that Congress abandoned past principles that sought to protect PMA holders' expectations that their PMA data would not be used by others to obtain approvals without an ample period of protection. The former version of §520 (h), which was enacted in 1990 and provided that PMA data could not be used by FDA (for the same purposes as those specified in section 216) until one year after the date of approval of a fourth device of a kind, provided specific retroactivity and procedures for defending a PMA holder's interest in data.<sup>5</sup> This provision sought to strike a balance between the absolute prohibiting or using PMA data included in "The Medical Device Amendments of 1976" and the availability of data after a reasonable time. Medtronic's data were not available for FDA's use under either the 1976 or 1990 amendments. Simply put, applying section 216 of FDAMA retroactively would be a departure from past law and the protection of companies such as Medtronic expected when deciding to market a device in the United States. The incentives and protections Congress placed in the law to encourage innovation would be frustrated by FDA illegally creating retroactivity based on the 1997 law.

Due to the lack of adequate publicly available valid scientific evidence supporting the petition, the Agency would have to rely on Medtronic's PMA data, particularly its manufacturing data, to make a decision on reclassification. Besides being protected by §520 (h) from use, Medtronic's data are also protected confidential commercial or trade secret information that may not be used by FDA to reclassify a device from Class III to Class I or II, [§520(c)]. Further, were the device to be reclassified into Class II, FDA would by necessity have to use Medtronic's PMA data to determine the substantial equivalence of 510(k) devices of the same generic type, thus effectively illegally using the data to support a reclassification. Simply put, there is no publicly available valid scientific evidence to support ANS' reclassification petition.

<sup>5</sup> Contemporaneously with the approval of the fourth device of a kind, the Secretary was to publish an order in the Federal Register identifying the four devices and the date that the information would be available for use by the Secretary. Challenges to the order announcing the availability of data for FDA's use had to be made within 30 days of its issuance. The intent of making disclosure dependent on approval of the fourth device of a kind was to provide protection to device firms commensurate with the size of their investment. As the time it would take to achieve four approvals would depend on the novelty and complexity of a device's technology, newer and more complex devices requiring greater time and expense to develop would receive substantial protection. For less ambitious, lower cost products, PMA approvals would occur more readily and less protection would result, [S. Rep. 513, 101<sup>st</sup> Cong. 2d Sess. 24, 25 (1990)].

3. **Procedural Irregularities Appear to Taint and Should Void the Panel's Recommendation**

There are several references in the transcript suggesting that a certain subset of panel members met before the panel meeting.<sup>6</sup> We understand that a meeting took place on the morning of the panel meeting. The industry representative and the Medtronic representative were not invited to the meeting. Under FDA's regulations implementing the Federal Advisory Committee Act ("FACA"), advisory committee meetings must be open to the public except under certain, very narrowly defined circumstances, (See 21 CFR §14.27). Portions of a meeting may only be closed if permitted under the Government in the Sunshine Act, which narrowly restricts closure, [see 21 USC 552b(c)], and the closed portion must be restricted to the shortest time possible. Moreover, at least 15 days prior to a meeting, notice of the meeting's agenda items and whether they will be discussed in an open or closed portion of the meeting, a statement of the time of the open and closed portions, and the reasons for closing any portion, among other things, must be published in the Federal Register, [21 CFR §14.20(b)]. The Federal Register Notice announcing this panel meeting stated that the meeting was closed to the public from 8:00-8:30 a.m. September 17, 1999, "to permit discussion and review of trade secret and/or confidential commercial information regarding pending and future FDA decisions," [64 *Fed. Reg.* 47843, 47844 (September 1, 1999)].

<sup>6</sup> E.g. speaker FDA's Dr. Bowsher stated "...that I've described frequently previously (page 153); they represent only totally implanted spinal cord stimulators or the Class II devices, were collected from the FDA web site," (page 154) (petition does not clarify this so ANS must have clarified it at the morning meeting); "As you have heard about preamendments...from training and everything else (page 248); As you have heard some in training...(page 265); maybe I gave this answer in one of the other sessions," (page 252). Finally, the following statement made by Dr. Canada, the Chairperson, was not found on the audio but was heard by two people present, and was edited out of the written transcript: "But this morning we discussed that," (*Attachment B*, pages 153,154,248,265,252).

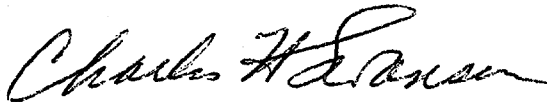
<sup>7</sup> Permissible reasons to close portions of meetings include review, discussion, and deliberation of internal agency documents, such as draft guidances and regulations, but only if their premature disclosure would significantly impede proposed agency action, and review of trade secrets and confidential commercial information, consideration of investigatory files compiled for law enforcement purposes, and review of matters, disclosure of which would constitute a clearly unwarranted invasion of personal privacy [21 CFR §14.27(b)(3)]. None of those reasons appear to apply here.

Compounding the lack of specificity regarding indications and the lack of crucial information about manufacturing procedures to adequately characterize the generic type, the absence of valid scientific evidence to determine risks and controls, and the procedural irregularities, was Ms. Maher's gross misstatement of the legal standard (that the Panel should be looking at the least burdensome way to get products on the market or at the lowest classification that will provide reasonable safety and effectiveness), which was insufficiently corrected in the ensuing discussion. The Panel was obviously confused. Instead of being required to overcome the presumption against down-classifying an implant and determine that Class III controls were unnecessary to ensure reasonable safety and effectiveness, the Panel was encouraged to employ lesser controls. The sheer number of controls recommended demonstrates the Panel's uncertainty and discomfort, as does the request for biennial inspection as a special control.

#### IV. Conclusion

In summary, there are a number of procedural irregularities and substantive deficiencies that require invalidation of the Panel's reclassification recommendation and that prohibit FDA from acting to reclassify totally implantable spinal cord stimulators into Class II. They are: (1) petitioner has not demonstrated that Class III controls are unnecessary to provide reasonable assurance of the safety and effectiveness of the device; (2) there is insufficient valid scientific evidence to demonstrate that Class II controls can provide a reasonable assurance of safety and effectiveness; (3) due to the irregularities in the proceedings the Panel was misinformed; (4) a breach of confidentiality entitled to Medtronic would occur if our PMA data was used improperly; and (5) FDA has ruled as recent as 1995 that the totally implantable spinal cord stimulator is a Class III device. For all the foregoing reasons we request that FDA deny ANS' petition for reclassification of Class III totally implanted spinal cord stimulators.

Sincerely,



CHS:kls:00012401.doc

cc:

Philip Phillips, FDA  
James Dillard, FDA

Attachment A:	ANS Petition
Attachment B:	Panel Transcript
Attachment C:	Dr. Susan Alpert Letter
Attachment D:	Dr. Richard North Letter

**Attachment A**  
**ANS Petition**



June 11, 1999

Food and Drug Administration  
Center for Devices and Radiological Health  
Office of Standards and Regulations (HFZ-84)  
5600 Fishers Lane  
Rockville, Maryland 20857

**Re: Section 513(f) Reclassification Petition**

Dear Sir/Madam:

The undersigned submits the enclosed petition in accordance with Section 513(f) of the Federal Food, Drug, and Cosmetic Act, (the "FDCA"), 21 U.S.C. § 360c(f) and regulations appearing in 21 C.F.R. § 860.123 to reclassify the device "Totally implanted spinal cord stimulator for pain relief" from class III into class II.

Since 1978 the device "Implanted spinal cord stimulator for pain relief" as identified in 21 C.F.R. § 882.5880 has been classified into class II (performance standards). This classification was accomplished in accordance with procedures described in Section 513 of the FDCA. No performance standards have been identified for application to this device. Prior to and at the time of classification, the direct current generator power source for this device was external to the implanted portions of this device. Subsequently, implanted generators were developed. Because implanted generator devices for spinal cord stimulators were not introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, Section 513(f) of the FDCA required classification into class III (premarket approval).

The only difference between "Implanted" and "Totally implanted" spinal cord stimulator devices is the location of the generator power source. Therefore, the petitioner believes that reasonable assurance of safety and effectiveness can be maintained through the application of special controls as authorized for class II devices since passage of the Safe Medical Devices Act of 1970.

The attached document is formatted in numerical order to address the specific reclassification content and form requirements outlined in 21 C.F.R. § 860.123.

Sincerely,

A handwritten signature in dark ink, appearing to read "Drew Johnson", with a long horizontal flourish extending to the right.

Drew Johnson  
Director, Regulatory Affairs  
Advanced Neuromodulation Systems, Inc.

**RECLASSIFICATION PETITION**  
**FOR**  
**TOTALLY IMPLANTED SPINAL CORD STIMULATOR**  
**FOR PAIN RELIEF**

**INTRODUCTION**

This petition is submitted in accordance with Section 513 (f) of the Federal Food, Drug, and Cosmetic Act (the "FDCA"), 21 USC § 360c(f) to reclassify the above referenced type of device from class III (premarket approval) to class II (special controls). This type of device is presently classified into class III by application of Section 513 (f) of the FDCA, because the implanted pulse generator (IPG) was not in commercial distribution prior to May 28, 1976, the effective date of this section of the FDCA.

**(1) SPECIFICATION OF THE TYPE OF DEVICE FOR WHICH RECLASSIFICATION IS REQUESTED**

Stimulator, Spinal Cord, Totally Implanted for Pain Relief

**(2) ACTION REQUESTED**

It is requested that Stimulator, Spinal Cord, Totally Implanted for Pain Relief device(s) be reclassified from class III to a class II under Section 513 (f) of the FDCA.

**(3) SUPPLEMENTAL DATA SHEET**

See attachment 1D

#### **(4) COMPLETED CLASSIFICATION QUESTIONNAIRE**

See attachment 1E

#### **(5) BASIS FOR DISAGREEMENT WITH THE PRESENT CLASSIFICATION STATUS**

Implanted spinal cord stimulators have been in commercial distribution since 1966 and formally classified into class II through notice and comment rulemaking by the Food and Drug Administration (FDA). Although the 1978 classification of the implanted spinal cord stimulator utilizing an external generator power source specified promulgation of a performance standard, no performance standard was ever proposed. Consequently the regulatory controls applicable to this type of device consisted of all the restrictions applicable to class I devices plus the requirement for biennial inspection. Review of the FDA experience associated with commercial distribution and use of these devices supports that the pervasive controls applicable to class II devices have been sufficient to provide the public with reasonable assurance of device safety and effectiveness.

The "totally implanted" spinal cord stimulator differs from the existing class II device identified in 21 C.F.R. 882.5880, because the generator power source is implanted rather than external. At least one totally implanted device has been in commercial distribution as a class III device for over 10 years. The safety and effectiveness performance of the totally implanted device as reflected by FDA documents available to the public and in the published literature support that the controls applicable to class II devices are adequate to provide reasonable assurance of safety and effectiveness.

While petitioner is required by regulation to express a statement of disagreement with the present classification as it is mandated by the FDCA, petitioner believes that representatives of the FDA and the public would agree that the pervasive regulatory controls applicable to class II devices when supplemented by appropriate special controls will provide reasonable assurance of safety and effectiveness. Finally, the authority vested in the FDA through the premarket notification requirement under section 510(k) of the FDCA represents the barrier to commercial distribution of any totally implanted device that is not substantially equivalent to the type of class II device identified and subject to special controls.

Since 1990, the 510(k) notification order has become the functional equivalent of a premarket approval (PMA) for certain devices. Unless the FDA issues an "order" of substantial equivalence, no totally implanted spinal cord stimulator can be lawfully made available in interstate commerce. Consequently, the "order" issued by the FDA for a class II device represents a premarket clearance by the FDA that is adequate to the needs of the public and facilitates the need for subsequent beneficial improvements to the device and competition.

#### **(6) FULL STATEMENT OF REASONS**

Devices that are used for pain relief through spinal cord stimulation require the surgical implantation of a receiver with electrodes. There are acceptable risks associated with any surgical procedure, but the benefit to the patient justifies the risk. Likewise, there are risks associated with the implantation of any device into the human body; and, some device implants such as prosthetic heart valves or cardiac pacemakers are intended to support or sustain life.

Thus the benefit clearly outweighs any foreseeable risk.

The implantation of a spinal cord stimulator for the relief of pain is not undertaken to support or sustain life, but it is essential to the quality of life for a patient. Moreover, as established by the 1978 classification into class II of implanted spinal cord stimulators, there is neither a potential unreasonable risk of illness or injury nor a use which is of substantial importance in preventing impairment of human health associated with the use of these devices. The implantation of the generator power source neither affects the intended use of the device nor alters the risk to the patient. The surgical risks associated with implantation of the receiver and electrodes is the same whether the generator power source is implanted or external. Spinal cord stimulation using both an IPG device or a radio frequency system has been proven to be safe and effective in treating a variety of chronic pain conditions. These include tumors, brachial plexus injuries, cord injury, phantom limb pain, reflex sympathetic dystrophy, ischemic limb pain, multiple sclerosis, peripheral vascular disease arachnoiditis, and pain after failed spine surgery (De la Porte and Siegfried, 1983; Kumar et al., 1986; Long and Erickson, 1975; Meglio et al., 1989; Ray et al., 1992; Siegfried and Lazorthes, 1982; Young, 1978).

Consequently, the special controls applicable to class II devices are abundantly sufficient to provide reasonable assurance of the safety and effectiveness of the spinal cord stimulator for which the generator power source is also implanted.

Consistent with the criteria for safety and effectiveness as described in 21 C.F.R. § 860.7, the petitioner has identified the benefits and risks associated with the implantation and use of all spinal cord stimulators irrespective of whether the generator is implanted or external.' This information as described below was derived from data maintained by the FDA and the published literature.

## Spinal Cord Stimulation (SCS) History

### ***SCS Background***

The use of electrical stimulation as a clinical tool has had a long history, which predates any apparent understanding of its mechanism of action. The first documented use of electrical stimulation was for the relief of pain from headaches and arthritis. Dioscorides, in 1559, reported that the marine torpedo could be applied on the skin to relieve prolonged headache (for review see Licht, 1996). Despite this long history, it wasn't until 1965 that Melzack and Wall first proposed a theory to explain the suppression of pain by electrical stimulation (Melzack and Wall, 1965). This theory, called the "gate control theory", proposed that the activation of low-threshold myelinated primary afferent fibers decreases the response of dorsal horn neurons to unmyelinated nociceptors (Melzack and Wall, 1965). Shealy et al., were the first to apply this theory in practice when they electrically stimulated the dorsal columns to treat chronic, intractable pain (Shealy et al., 1967). Since the first implant, dorsal column stimulation (or spinal cord stimulation, SCS) has been applied to a wide variety of painful disorders. These include tumors, brachial plexus injuries, cord injury, phantom limb pain, reflex sympathetic dystrophy, ischemic limb pain, multiple sclerosis, peripheral vascular disease arachnoiditis, and pain after failed spine surgery (De la Porte and Siegfried, 1983; Kumar et al., 1986; Long and Erickson, 1975; Meglio et al., 1989; Ray et al., 1992; Siegfried and Lazorthes, 1982; Young, 1978). It has been estimated that 12,000 SCS systems are sold every year world-wide (Linderorth and Myerson, 1995).

### ***Possible Mechanisms***

Although, first inspired by the gate theory (Melzack and Wall, 1965), spinal cord stimulation is now linked to several other mechanisms. It has been found to activate spinal pain inhibitory

circuits, mainly those concerned with the GABAergic and adenosine transmission (Lundeberg, 1996; Cui et al., 1997; 1998). After peripheral nerve injury, levels of excitatory amino acids (EAA), mainly glutamate and aspartate, have been found to increase in the dorsal horn (Al-Ghoul et al., 1993; Castro-Lopes et al., 1993). Experiments performed on rats have found that SCS induces a decreased release of the EAA, associated with an increase in the release of GABA and adenosine (Cui et al. 1997; 1998). This SCS induced response can be transiently abolished by local perfusion with a GABA<sub>B</sub>-receptor or an adenosine A<sub>1</sub> receptor antagonist. Cui and colleagues have proposed that the effect of SCS on neuropathic pain and allodynia may be due to an activation of local GABAergic mechanisms inhibiting the EAA release. More recently, they have found that SCS treatment in patients previously found to be non-responders can be enhanced by combining SCS therapy with the infusion of either baclofen (a GABA agonist) or adenosine. Other theories have suggested that electrical stimulation of the spinal cord may produce analgesia through a frequency-related conduction block (Campbell et al. 1981).

SCS has also been shown to have an affect at the cerebral level (Hosobuchi 1985; Hautvast et al., 1997). Hautvast et al. found that SCS increased regional cerebral blood flow in the left ventrolateral periaqueductal grey, the medial prefrontal cortex, the dorsomedial thalamus bilaterally, the left medial temporal gyrus, the left pulvinar of the thalamus, bilaterally in the posterior caudate nucleus, and the posterior cingulate cortex. In both experimental animal studies and human studies SCS induces peripheral vasodilatation, although the exact mechanism is under debate (Croom et al., 1997; Linderoth et al., 1995).

### ***Patient Selection***

Spinal cord stimulation systems are relatively simple to implant, with many of the stimulation parameters under patient control. This has led to its use in a wide array of painful conditions without regard to the etiology or pathophysiology (De La Porte and Van de Kelft, 1993). Thus,

numerous reports have success rate of fewer than 25%. According to the European Group for the Study and Treatment of Pain, only 23% of the preliminary cases reported long-lasting pain relief using SCS (Krainick, 1984). The main reason for this low success has been the diverse group of pain conditions typically treated with SCS and the weak patient selection criteria that have been used. Only recently have more stringent selection criteria been followed. It is now recognized that the most appropriate patients for SCS are those with chronic, nonmalignant pain of neuropathic origin (Simpson, 1994). Another important selection criterion is psychological attitude. Patients are now routinely screened to eliminate those patients with major personality disorders, secondary gain issues, or drug abuse problems (Randolph, 1998; Gamsa, 1994; Burchiel, 1995).

Improved patient selection has increased the success rate of SCS. A recent report of the results of a series on failed back surgery syndrome and neuropathic pain of peripheral origin has shown good long-term outcome in 50-60% of cases treated (Turner, 1995; Burchiel, 1996). Kumar et al. report that SCS is an effective therapy for pain syndromes associated with peripheral neuropathy. However, they conclude that patients with postherpetic pain and intercostal neuralgia do not obtain long-term benefit with SCS. Numerous reports have shown success when using spinal cord stimulation to treat the pain from reflex sympathetic dystrophy (or complex regional pain syndrome I) (Kemler, 1999; Calvillo et al., 1998; Kumar et al., 1997). A recent report by Stanton-Hicks et al. included neuromodulation in the guidelines for therapy for complex regional pain syndromes (Stanton-Hicks et al., 1998). Spinal cord stimulation has also been found to be highly effective in treating the pain from angina and peripheral vascular disease (Eliasson, 1996; Kumar, 1997). A recent report suggests that the efficacy of spinal cord stimulation in the treatment of pain for angina is similar to that of coronary artery bypass surgery (Mannheimer, 1998). Patients with peripheral vascular disease have had success rates of 50-

80% for the relief of pain, with evidence of improved circulation (Kumar et al., 1997; Jivegard et al., 1995). With careful patient screening and improved technology, spinal cord stimulation may prove even more effective in the future.

### ***SCS Systems***

Two different SCS systems are routinely used, including those systems that use percutaneously placed electrode leads or those that require laminectomies to place the electrodes. The former involves the percutaneous insertion of electrodes into the epidural space. The lead from the electrodes may then be connected to an external generator, allowing a trial period of stimulation, or it may be connected subcutaneously to an implanted radio frequency (RF) controlled receiver or to a totally implanted pulse generator (IPG).

Paddle type leads require implantation into the epidural space via laminectomy. The leads are then connected subcutaneously to a radio-controlled receiver or an IPG. The RF-controlled receiver is activated by an external battery-powered transmitter, which operates through an antenna placed over the receiver. The IPG contains a battery, which supplies power to the electrodes.

Although the RF receiver is a class II device and the IPG is currently a class III device, the only difference between the two SCS devices is that the IPG has an internal power source while the RF receiver does not.

### ***Surgical Procedure***

To effectively treat pain, a spinal cord stimulation system must have the potential to target the anatomic areas where the patient feels pain. The target area must be provided with pain-relieving paresthesia at tolerable and patient adjustable intensity levels.

With the patient under local anesthesia, a small puncture is made in the skin with a paramedian approach at an angle of no more than 30-40 degrees. An epidural needle is inserted and confirmed as having entered into the epidural space. Using fluoroscopic guidance, a lead blank (a lead without any electrodes) is inserted through the needle into the dorsal epidural space, and is manipulated to establish an appropriate pathway. The lead is then introduced into the epidural space, either through the needle or through the use of a lead introducer. Proper lead placement is verified through intraoperative trial stimulation, in which paresthesia is experienced by the patient. Upon verification of proper lead placement, the lead is secured using a lead anchor and sutures.

The IPG / receiver is implanted by making a pocket incision at the desired location, and creating a subcutaneous pocket by blunt dissection to accommodate the receiver. A subcutaneous tunnel is made from the lead incision site to the IPG/receiver implantation site, using a tunneling tool, and the lead is tunneled to the IPG/receiver site. The lead is connected to the IPG/receiver, the IPG/receiver is placed in the subcutaneous pocket, and the incisions are closed.

### **Risks associated with Spinal Cord Stimulation**

A list of the reported complications for all spinal cord stimulator devices by author is found on Table 1A and 1B. The first report listed, by Turner et al. summarizes the findings of 39 English and French language articles reporting on the use of SCS between the years 1966-June 1994. Fourteen of these articles were published before 1983 (Turner et al., 1995). The articles were chosen to include studies that provided at least 30 days of follow-up for the patients, and included data from patients with chronic low back and lower extremity pain following prior

surgery (Failed Back Surgery Syndrome). Most of the complications were minor consisting of electrode migration, lead wire complications or difficulty with the pulse generator.

The remaining summary of the available literature was obtained through a MEDLINE search using the key words "spinal cord stimulation" or "dorsal column stimulation" and "pain" for the years 1983 to present. This search yielded a total of 253 papers of which 31 English language papers were found to list complications irrespective of whether the power generator was implanted or external. Tables 1A and 1B includes lead migration, infection, epidural hemorrhage, seroma, hematoma, paralysis, cerebral spinal fluid (CSF) leak, over/under stimulation, intermittent stimulation, pain over the implant, allergic reaction, skin erosion, lead breakage, hardware malfunction, loose connection, other, biologic reaction specific to an IPG, and battery failure.

Five papers listed in the summary were also included in the Turner review. These include Meglio (1989), Probst (1990), Wester (1987), LeDoux (1993), and De La Porte (1993).

MDR report data for IPG devices was collected from the FDA website at <http://www.fda.gov/cdrh/mdrfile.html>, where records were sorted into the years 1984 through 1996. Data for each year was compressed into files, which were downloaded and put into a database (Table 2). Attempts to download information from 1991 were unsuccessful due to a minor glitch in the FDA's database for that particular year. The petitioner believes that the absence of the information for 1991 does not significantly impact the overall MDR data analysis in this petition. Each report was treated as an individual record in the database. Once in the database, searches could be performed for reports from a certain product, manufacturer, or date.

For incident reports occurring after 1996, a search engine at the FDA MAUDE site was used, <http://www.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.cfm>. Multiple criteria could be used simultaneously for MAUDE searches, thus returning more applicable information.

#### ***A. Lead migration:***

Lead migration is the most common risk associated with SCS and occurs when the lead moves out of its position. Lead migration results in a loss of proper paresthesia coverage and a subsequent reduction in pain relief. Turner et al. found that 16 of the 39 papers reviewed provided data regarding lead migration (Turner et al., 1995). They found that 24% of the patients in these 16 studies required either reoperation or reprogramming due to lead migration. Table 1A shows the results of 32 papers reporting complications. All but three of the papers reported lead migration as one of their complications. Analysis of this series gave a lead migration rate of 14.6%.

Andersen reported on the use of SCS for angina (Anderson, 1997). He found the most frequent complication that required reoperation was lead migration (23%). The incidence was statistically lower in patients with quadripolar leads (11%) than in patients with monopolar electrodes (45%,  $p < 0.003$ ). There was no difference in the frequency of migration of electrodes between the two types of electrodes. North et al. reported on the use of SCS in 62 chronic pain patients (North et al., 1991). They found that surgical revision was necessary in 23% of the cases with simple bipolar leads to obtain optimal paresthesia coverage. However, surgical revision was required in only 16% of those cases with "multi-channel" devices.

The introduction of multichannel leads has greatly reduced the need for reoperation as the result of lead migration. A report by North et al. found that programmable, multichannel systems have a significantly greater clinical reliability than single-channel systems (North et al., 1991). Alo et

al. reported that only 3.8% of their patients required revision of lead placement to improve capture, and the remaining 96.2% of the patients who lost paresthesia were able to regain it by reprogramming. He claimed this was the result of using the eight-electrode lead and complex programming (Alo et al., 1998).

Through analysis of the publicly available MDR data (n=408), there was only one occurrence in which lead migration led to an explantation. Other cases in which lead migration resulted in a loss of stimulation were remedied through reprogramming of the device. Both RF and IPG systems have reprogramming capabilities.

The special controls available for this risk include the following: the labeling guidance Medical Device Labeling: Suggested Format and Content, international standards such as EN 1441, Medical Device Risk Analysis, and FDA Guidance Documents for Design Control Guidance for Medical Devices. See the attached Special Control Chart-Table 1C.

The petitioner proposes the use of an adverse event warning in the labeling to state: "Adverse events include migration" as the special control for this risk.

***B. Infection, epidural hemorrhage, seroma, hematoma and/or paralysis:***

As with any surgical procedure the risk of infection is a possible adverse event. Although most infections that occur as result of a SCS implantation can be resolved either with antibiotics or with the removal of the SCS unit followed by antibiotics, life-threatening infections can occur. A report by Torrens et al. described one such case. This particular patient was found to have methicillin-resistant *Staphylococcus aureus* (MRSA) infection. Torrens suggests that the patient population typically identified for SCS systems have a higher risk of MRSA infection due to frequent and prolonged hospitalization for severe neuropathic pain and courses of antibiotics for

various infections. In addition, he points out that patients with diabetes mellitus have an increased susceptibility to infection. He suggests that screening for MRSA colonization would help in identifying patients at risk for infection (Torrens et al., 1997).

There has been one report of a bacterial infection located at the lead tip resulting in paralysis (Meglio et al., 1989). A myelographic block was found at the level of the electrode tip. An operation revealed a bacterial epidural and intradural abscess that was removed. The patient recovered well but not completely. Although, paralysis is a possible risk, only 1 case was found in the 2075 cases reviewed in Table 1. As with any surgical procedure involving implantation in the epidural space, paralysis is a possible adverse event regardless of whether the SCS system has an internally or externally powered device.

The average infection rate reported by Turner et al. was 5% from 20 papers. This is similar to the 4.5% infection rate reported in Table 1.

Meglio et al. reported three bacterial infections as the result of SCS, with two occurring at the electrode site and one at the subcutaneous pocket (Meglio et al. 1989).

Another complication that has been reported following the implantation of an SCS system is a hematoma. This was found to occur in only 5 cases out of 1984. Three cases of subcutaneous hematoma were reported by Meglio (Meglio et al., 1989). Subcutaneous hematoma may occur regardless of whether the system is a RF or IPG device. All three patients were undergoing anticoagulation therapy. None of the papers summarized in Table 1 reported epidural hemorrhage or seroma.

Of the 408 total MDR reports utilized, there were 14 events of infection (3.43%) and only one of seroma (0.25%) found. There were no reports of epidural hemorrhage, hematoma, or paralysis.

The special controls available for these risks include the labeling guidance Medical Device Labeling: Suggested Format and Content, 510(k) Sterility Review Guidance, Sterilization validation standard- AAMI/ISO11135, international standards such as EN 1441, Medical Device Risk Analysis. See the attached Special Control Chart-Table 1C.

The petitioner proposes the use of an adverse event warning in the labeling to state: "Adverse events include infection, epidural hemorrhage, seroma, hematoma and/or paralysis" as the special control.

### ***C. CSF leakage:***

Cerebral spinal fluid (CSF) leaks occur following accidental dural puncture with either the epidural needle, guide wire (lead blank) or leads during the surgical procedure. A CSF leak can lead to a headache, which usually occurs in the early postoperative period and which characteristic features are those of a headache that may be frontal or occipital, relieved by recumbency, and accompanied by tinnitus, diplopia, neck pain and nausea. The cause of the headache is thought to be the result of decreased hydraulic support for intracranial structures (Brownridge, 1983). Small dural punctures usually heal spontaneously and the headache can be treated conservatively (Kumar, 1991). The injection of autologous blood into the patient's epidural space is commonly used to treat postdural postural headache if conservative measures are unsuccessful (DiGiovanni, 1970).

Of the 32 articles reviewed in Table 1 only 6 cases of CSF leaks were reported. This type of incident may occur regardless of whether the device is an IPG or RF system. Overall the incidence of CSF leaks is very small occurring in only 0.3% of the time.

There were no cases of CSF leakage found in the MDR search.

The special controls available for this risk include the labeling guidance Medical Device Labeling: Suggested Format and Content, international standards such as EN 1441, Medical Device Risk Analysis. See the attached Special Control Chart-Table 1C.

The petitioner proposes the use of an adverse event warning in the labeling to state: "Adverse events include CSF leakage", as the special control for this risk.

***D. Undesirable changes in stimulation over time:***

Changes in stimulation may occur over time. These changes can be the result of cellular changes in tissue around the electrodes or temporary changes in the electrode position. Reports of painful stimulation have been found in the literature as well as those cases of ineffective stimulation or loss of stimulation over time. The literature search summarized in Table 1A found eleven cases of either over or under stimulation. This type of incident may occur regardless of whether the device is an IPG or RF system. No cases of intermittent stimulation were observed.

Burchiel et al. reported seven cases of undesirable changes in stimulation over time. These included ineffective pain control with stimulation (n=5), change in stimulation pattern (n=1), and decreased stimulation (n=1) (Burchiel et al. 1996). Meglio et al. reported on two cases that complained of pinprick-like pain at the electrode site (Meglio et al. 1989). The last two cases that reported changes in stimulation were from a study by Mittal et al. They reported two cases of increased discomfort. In one of the patients the rate dial had been inadvertently increased, while in the second case the patient had repeatedly turned the system to full amplitude (Mittal et al. 1987).

A total of 106 of the available MDR cases involved changes in stimulation. This type of incident may occur regardless of whether the device is an IPG or RF system. These include 50 events of intermittent stimulation (12.25%), 33 of overstimulation (8.09%), and 23 shock (5.64%)

The special controls available for this risks include the labeling guidance Medical Device Labeling: Suggested Format and Content, international standards such as EN 1441, Medical Device Risk Analysis, EN/IEC 60601 series, ANSI/AAMI NS14-1995 Implantable Spinal Cord Stimulators, EN 45502-1 Active Implantable Medical Device – General Requirements for Safety. See the attached Special Control Chart-Table 1C.

The petitioner proposes labeling special controls utilizing adverse events/warning/precautions in the labeling to state: "Adverse events include undesirable changes in stimulation", Warning: "Patients should not drive or use dangerous equipment during stimulation". Adverse Event: "Loss of stimulation" Precautions: "Systems maybe affected by or adversely affect cardiac pacemakers, cardioverter/defibrillators, external defibrillators, MRI, diathermy, ultrasonic equipment electrocautery, radiation therapy, theft detectors, security systems, and aircraft communication systems".

#### ***E. Pain at the sites over the implanted system components:***

Whenever there is a disruption of body tissue temporary pain results. This temporary pain is due to the healing process. The usual location of the pain after a SCS implant is at the incision site. However, pain can also occur at the site of the implant. This type of pain usually subsides after 7 to 14 days. The actual tissue reaction resolves within 2 to 3 weeks. Occasionally, tenderness can occur over the receiver site or the connector at the spinous process, which does not resolve with time. In many cases this tenderness does not require removal of the unit. Pain over the implant was found to occur in 20 of the 1924 cases summarized in Table 1A. This type of

incident may occur regardless of whether the device is an IPG or RF system. Most of these cases did not require reoperation. When reoperation did occur, repositioning the receiver usually diminished the pain (Burchiel, 1996).

Burchiel et al. reported on four cases of pain or burning along the lead/pulse generator that did not require reoperation and two cases that required repositioning of the pulse generator (Burchiel et al. 1996). Le Doux and Langford reported on four cases of pain at the receiver site, which required reoperation (Le Doux and Langford, 1993). Barolat et al. found four cases of prolonged pain at the surgical sites (Barolat et al. 1989). Three cases, reported by Ohnmeiss et al., required a repositioning of the stimulator because the unit was originally implanted under the patients' beltlines (Ohnmeiss et al. 1996). Segal et al., Rossi and Rabar, and Wester each, reported on one case of discomfort over the receiver (Segal et al., 1998; Rossi and Rabar, 1994; Wester, 1987).

Pain at the implant site requiring explantation has occurred only 10 times (2.45%) of the 408 total cases in the MDR search.

The special controls available for this risks include the labeling guidance Medical Device Labeling: Suggested Format and Content, international standards such as EN 1441, Medical Device Risk Analysis, See the attached Special Control Chart-Table 1C.

The petitioner proposes utilizing an adverse event warning in the labeling to state: "Adverse events include possible pain at the implant site" as the special control.

#### ***F. Allergic or rejection response to implanted materials:***

Although all the materials that come in contact with human tissue have been confirmed to be biocompatible there have been documented cases of allergic reactions. Allergic reactions occur

when there is an immune reaction to a foreign substance. When an allergic reaction does occur after the implantation of an SCS system, the implanted device must be removed. This type of risk is very rare. Table 1B shows 3 cases out of 1924 that reported an allergic reaction. All of these reactions occurred with the lead material, and required removal of the device (Meglio et al., 1989; Barolat et al., 1989).

There has been only one (0.25%) reported incident, out of 408 MDRs, involving an allergic reaction to an IPG system. This reaction was determined to be to the titanium case. Titanium has been well documented as a safe material for implant applications.

The special controls available for this risk include the labeling guidance Medical Device Labeling: Suggested Format and Content, international standards such as EN 1441, Medical Device Risk Analysis, Consensus Standard EN/ ISO 10993 – Biological Evaluation of Medical Devices – Part 1, and ASTM F67-95 Standard for Unalloyed Titanium. See the attached Special Control Chart-Table 1C.

The petitioner proposes utilizing an adverse event warning in the labeling to state: "Adverse events include allergic response" as the special control.

***G. Local skin erosion over the implanted receiver:***

Diabetic peripheral neuropathy can result in pain of the extremities and has become an indication for the use of SCS. However, peripheral neuropathy can also result in skin problems, which can be exacerbated by an implant. When skin erosion can be attributed to the IPG or receiver they usually require removal. This type of incident may occur regardless of whether the device is an IPG or RF system. Skin erosion was found to occur in 3 of the 1924 cases examined. Ohnmeiss et al. described one patient with diabetic peripheral neuropathy who

required the removal of the unit due to local skin erosion, however, the skin problem resolved and a SCS unit was eventually replaced (Ohnmeiss et al., 1996). Rossi and Rabar described two cases of skin erosion at the receiver site, which resolved after debridement (Rossi and Rabar, 1994).

Two events involving skin erosion have been reported through MDR research, which is only 0.49% of the total MDRs.

The special controls available for this risk include the labeling guidance Medical Device Labeling: Suggested Format and Content, international standards such as EN 1441, Medical Device Risk Analysis. See the attached Special Control Chart-Table 1C.

The petitioner proposes utilizing an adverse event warning in the labeling to state: "Adverse events include erosion" as the special control.

#### ***H. Device failure:***

Device failure can be broken down into several subsets, including electrode breakage, hardware malfunction and loose connections. Device failures occurred in 144 of the 1924 cases (7.5%-see table 1B). Seventy-nine of these failures were the result of lead breakage and sixty-four were the result of hardware malfunctions and one was the result of a loose connection. These types of events may occur regardless of whether the device is an IPG or RF system.

Device failure was identified in 63 of the 408 MDRs. Loose connections (n=4), broken leads (n=15), and other hardware malfunctions (n=44) have occurred in 0.98%, 3.68% and 10.78% of the total MDRs respectively.

The special controls available for this risk include consensus standards such as EN 1441, Medical Device Risk Analysis, EN/IEC 60601 series, ANSI/AAMI NS14-1995 Implantable Spinal Cord Stimulators, EN 45502-1 Active Implantable Medical Device – General Requirements for Safety. See the attached Special Control Chart-Table 1C.

The petitioner proposes the consensus standard ANSI/AAMI NS14 -1995 Implantable Spinal Cord Stimulators and EN 45502-1 Active Implantable Medical Devices – General Requirements for Safety to be used as the special controls. See the attached Special Control Chart-Table 1C.

#### *I. Other:*

Various risks were found that did not fit into any of the above categories (12 out of 1984 cases). Two patients reported to have developed a psychosis as the result of an implant (Calvillo, 1998; Zdanowicz, 1999), which required the removal of the SCS system. There have also been reports of muscle spasm (N=1) and urinary hesitancy (N=1) (Burchiel et al., 1996).

Barolat et al. reported on one patient who had excessive positional changes in the stimulation threshold (Barolat et al., 1989). Paresthesiae were felt when lying in the supine position, but were greatly reduced when standing or sitting. Studies have found that the thresholds for stimulation are highest in the thoracic level (He et al. 1997). They have also found the largest usage range to be at this level. However, this range varies greatly between patients and between postures. A recent study by Cameron et al. studied the effects of posture of patient previously implanted with a percutaneous SCS lead (Cameron et al., 1998). In twenty patients the threshold for paresthesia was lowest when lying, while in three patients it was lowest when sitting. The mean range and standard error of stimulation required to achieve paresthesia at all three posture levels was found to be  $.51 \pm .2 \mu\text{C}$  for leads in the cervical region (N=11) and  $1.52 \pm .2 \mu\text{C}$  for leads in the thoracic region (N=19).

There have been some recent reports of interference that occurs when a patient with an SCS system enters an electromagnetic field created by a security system. In one such case the patient experienced permanent neurological injuries due to the uncontrolled activation of the cervical SCS device (Eisenberg, 1997).

One patient reported by Mittal et al. suffered from a mild pulmonary embolism which occurred 10 days after the insertion of a permanent RF system (Mittal et al., 1987). This patient recovered with conservative therapy and the device was left in place.

There have been seven reported cases of aseptic meningitis associated with the implantation of an SCS system (Meglio et al. 1989; 1991; Cioni et al. 1995). All cases resolved without any permanent damage. Two of the cases resolved spontaneously, while the remaining five cases required the removal of the system. All reported cases of aseptic meningitis came from the same center.

Headache, asthenia, and dizziness occurred during stimulation in five patients. In two patients with spinal cord lesion, SCS increased muscle spasms. Muscle twitches due to radicular stimulation were described by three patients, and in one patient muscular contraction due to activation of the pyramidal tract was observed (Meglio et al., 1989)

The largest single category of MDRs were classified as other (n=144) due to a lack of reported information.

The special controls available for these risks include the labeling guidance Medical Device Labeling: Suggested Format and Content. See the attached Special Control Chart-Table 1C.

The petitioner proposes labeling special controls utilizing an adverse event warning/precaution statement in the labeling to state: Warning: "Other adverse events include headache, asthenia, and dizziness". Precaution: "Systems maybe affected by theft detectors or security systems".

## **Risks Associated with the Implanted Pulse Generator (IPG)**

### **J. Battery Failure:**

The battery of an IPG is located within the device, therefore when the battery is depleted replacement requires reoperation. When a battery requires replacement before the expected date (usually 2 to 3 years) it is considered a battery failure. Battery failure occurred in 28 of the 1538 cases or 1.8% of the time, although in 22 out of 28 cases the battery failure occurred after more than 3 years (see table 1B).

Nine studies reported on reoperation due to battery depletion. De La Porte and Van de Kelft and Fiume et al. each reported on eight cases of battery depletion (De La Porte and Van de Kelft, 1993; Fiume et al., 1995). Meglio et al. reported on four cases, Francaviglia et al. reported on two cases, that required reoperation due to battery depletion (Meglio et al., 1994; Francaviglia et al., 1994). The average follow-up period for all these studies was greater than the average expected battery life (approximately three years).

Meglio et al. reported on a case in which early battery depletion occurred, however, this patient required a very high current intensity to achieve paresthesia (Meglio et al., 1989). Burchiel et al. reported on two cases in which the battery depleted in less than one year, but no data regarding the usage were reported (Burchiel et al., 1996). Ohnmeiss et al. reported on one case that required battery replacement after 18 months probably due to continuous use of the system (Ohnmeiss et al., 1996). Segal et al. reported on a patient who kept the stimulator on 24 hours a

day and required battery replacement after only one year (Segal et al., 1998). Finally, Graziotti and Goucke reported a case study on a patient who used the device 24 hours per day and depleted the battery after one year (Graziotti and Goucke, 1993).

Battery failure was reported in 66 MDRs.

The special controls available for this risk include consensus standards such as EN 1441, Medical Device Risk Analysis, EN/IEC 60601 series, ANSI/AAMI NS14-1995 Implantable Spinal Cord Stimulators, EN 45502-1 Active Implantable Medical Device – General Requirements for Safety and labeling guidance Medical Device Labeling: Suggested Format and Content. See the attached Special Control Chart-Table 1C.

The petitioner proposes utilizing a chart in the labeling that estimates the life of the battery under specific power consumption conditions be used as the special control.

**(7) UNFAVORABLE REPRESENTATIVE DATA AND INFORMATION TO THE PETITIONER'S POSITION.**

The literature review did not find any negative articles that would require a totally implanted spinal cord stimulator for pain relief device to remain in class III. The main difference between an implanted pulse generator device and an RF device is the internal battery. The limited battery life of an IPG requires that it is used in situations that require moderate to low power consumption, however, this limitation does not reduce the safety of the device.

**(8) NEW INFORMATION UNDER SECTION 513(e), 514(b), OR 515(b) OF THE ACT**

Not applicable

## **(9) NEW INFORMATION SOURCE DOCUMENTS**

Not applicable

## **(10) FINANCIAL DISCLOSURE STATEMENT**

Among the published literature studies identified in support of this petition, only 3 involved participation by individuals listed in tables 1A and 1B who had a financial relationship with the petitioner prior to publication. The relationships ranged from employment to compensation associated with performance of a clinical investigation and may have included either stock ownership or options for stock purchase.

All of these published literature studies were completed prior to the February 2, 1999 effective date of this regulation. There are no covered clinical studies ongoing as of February 2, 1999 which the petitioner relies on to establish device effectiveness or a significant contribution to the demonstration of safety in relation to this reclassification petition.

The petitioner does not intend to submit any clinical studies because of its reliance on the published literature. Therefore the petitioner believes that the provisions of 21 C.F.R. Part 54 relating to financial disclosure are not applicable.

## **SUMMARY**

The petitioner believes that compliance with provisions of the FDCA applicable to class II devices, including the requirement for obtaining a premarket notification order from the FDA, is sufficient to provide reasonable assurance of the safety and effectiveness of totally implanted spinal cord stimulator devices for pain relief. This assurance is enhanced through the

requirement for compliance with special controls as demonstrated through the premarket notification process implemented through manufacturing compliance during commercial distribution, and confirmed by FDA surveillance activities.

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Author	A	B					C	Over/under Stim	Intermittent Stim
	Lead Migration	Infection	Epidural Hemorage	Seroma	Hematoma	Paralysis	CSF Leak		
Turner et al. 1995*	24%/16	5%/20							
Tesfaye et al. 1996	2/8	2/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8
Ohnmeiss et al. 1996	4/40	1/40	0/40	0/40	0/40	0/40	0/40	0/40	0/40
Burchiel et al. 1996	3/70	3/70	0/70	0/70	0/70	0/70	1/219	7/70	0/70
Kumar et al. 1996	4/19	1/19	0/19	0/19	0/19	0/19	0/19	0/19	0/19
Calvillo et al. 1998	2/31	2/31	0/31	0/31	0/31	0/31	0/31	0/31	0/31
Kemler et al. 1999	7/18	2/18	0/18	0/18	0/18	0/18	0/18	0/18	0/18
Kumar and Toth 1998	55/165	9/165	0/165	0/165	0/165	0/165	1/165	0/165	0/165
Fiume et al. 1995	6/36	5/36	0/36	0/36	0/36	0/36	0/36	0/36	0/36
Alo et al. 1998	3/80	4/80	0/80	0/80	0/80	0/80	0/80	0/80	0/80
Segal et al. 1998	1/24	0/24	0/24	0/24	0/24	0/24	0/24	0/24	0/24
Kumar et al. 1998	64/189	10/235	0/189	0/189	1/189	0/189	0/189	0/189	0/189
Francaviglia et al. 1994	0/15	0/15	0/15	0/15	0/15	0/15	0/15	0/15	0/15
Meglio et al. 1994	1/21	3/21	0/21	0/21	0/21	0/21	1/21	0/21	0/21
Broggi et al. 1994	16/363	5/363	0/363	0/363	0/363	0/363	0/363	0/363	0/363
Rossi and Rabar 1994	4/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Robaina et al. 1989	2/11	1/11	0/11	0/11	0/11	0/11	0/11	0/11	0/11
Barolat et al. 1989	2/18	0/18	0/18	0/18	0/18	0/18	0/18	0/18	0/18
Sanchez-Ledesma et al. 1989	1/36	1/36	0/36	0/36	0/36	0/36	0/36	0/36	0/36
Westner 1987	0/30	2/30	0/30	0/30	0/30	0/30	0/30	0/30	0/30
Demirel et al. 1984	11/33	4/33	0/33	0/33	0/33	0/33	1/33	0/33	0/33
Meglio et al. 1989	3/64	3/109	0/109	0/109	3/109	1/200	2/109	2/64	0/64
North et al., 1993	0/298	15/298	0/298	0/298	0/298	0/298	0/298	0/298	0/298
Mittal et al., 1987	2/35	3/35	0/35	0/35	0/35	0/35	0/35	2/35	0/35
Racz et al., 1989	18/26	2/26	0/26	0/26	1/26	0/26	0/26	0/26	0/26
Graziotti and Goucke, 1993	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
LeDoux and Langord, 1993	10/23	0/23	0/23	0/23	0/23	0/23	0/23	0/23	0/23
Hasswnbusch et al., 1995	5/26	0/26	0/26	0/26	0/26	0/26	0/26	0/26	0/26
Cioni et al., 1995	1/10	1/25	0/25	0/25	0/25	0/25	0/25	0/10	0/10
DeLa Porte and VandeKelft, 1993	8/64	5/64	0/64	0/64	0/64	0/64	0/64	0/64	0/64
Probst, 1990	20/92	5/92	0/92	0/92	0/92	0/92	0/92	0/92	0/92
Kumar et al., 1997	2/12	0/12	0/12	0/12	0/12	0/12	0/12	0/12	0/12
Waisbrod, and Gerbershagen, 1985	5/16	1/16	0/16	0/16	0/16	0/16	0/16	0/16	0/16

Total	275/1924	91/2030	0/1984	0/1984	5/1984	1/2075	6/1984	11/1924	0/1924
%	14.2	4.48	0	0	.25	.05	.3	.6	0

Table 1A: This table shows the number of occurrences over the total number of implants for each of the studies cited. \*This paper is a review of 39 articles the numbers in this row are the average percentages of each occurrence over the total number of studies.

Note: Citations cover both IPG and RF Systems

Author	E Pain over implant	F Allergic Reaction	G Skin Erosion	H Lead Breakage	H Hardware Malfunction	I Loose Connection	I Other	K Battery Failure
Turner et al 1995.*				7%/15				2%/14
Tesfaye et al. 1996	0/8	0/8	0/8	0/8	0/8	0/8	0/8	N/A
Ohnmeiss et al. 1996	3/40	0/40	1/40	0/40	0/40	0/40	0/40	1/40
Burchiel et al. 1996	6/70	0/70	0/70	1/70	4/70	0/70	2/70	2/70
Kumar et al. 1996	0/19	0/19	0/19	2/19	2/19	0/19	0/19	0/19
Calvillo et al. 1998	0/31	0/31	0/31	0/31	0/31	0/31	1/31	0/31
Kemler et al. 1999	0/18	0/18	0/18	1/18	1/18	0/18	0/18	0/18
Kumar and Toth 1998	0/165	0/165	0/165	6/165	6/165	0/165	0/165	0/165
Fiume et al. 1995	0/36	0/36	0/36	3/36	0/36	0/36	0/36	8/36
Alo et al. 1998	0/80	0/80	0/80	0/80	0/80	0/80	0/80	N/A
Segal et al. 1998	1/24	0/24	0/24	1/24	0/24	0/24	0/24	1/24
Kumar et al. 1998	0/189	0/189	0/189	8/189	8/189	0/189	0/189	0/189
Francaviglia et al. 1994	0/15	0/15	0/15	0/15	0/15	0/15	0/15	2/15
Meglio et al. 1994	0/21	0/21	0/21	4/21	2/21	0/21	2/21	4/21
Broggi et al. 1994	0/363	0/363	0/363	6/363	0/363	0/363	0/363	0/363
Rossi and Rabar 1994	1/50	0/50	2/50	4/50	2/50	0/50	0/50	0/50
Robaina et al. 1989	0/11	0/11	0/11	0/11	0/11	0/11	0/11	0/11
Barolat et al. 1989	4/18	1/18	0/18	3/18	0/18	0/18	1/18	0/18
Sanchez-Ledesma et al. 1989	0/36	0/36	0/36	0/36	0/36	0/36	0/36	0/36
Westner 1987	1/30	0/30	0/30	0/30	0/30	0/30	0/30	0/30
Demirel et al. 1984	0/33	0/33	0/33	0/33	3/33	0/33	0/33	0/33
Meglio et al. 1989	0/64	2/64	0/64	0/64	4/64	0/64	4/109	1/64
North et al., 1993	0/298	0/298	0/298	22/298	16/298	0/298	0/298	N/A
Mittal et al., 1987	0/35	0/35	0/35	4/35	0/35	0/35	1/35	0/35
Racz et al., 1989	0/26	0/26	0/26	6/26	3/26	0/26	0/26	0/26
Graziotti and Goucke, 1993	0/1	0/1	0/1	0/1	0/1	0/1	0/1	1/1
LeDoux and Langford, 1993	4/23	0/23	0/23	0/23	4/23	1/23	0/23	0/23
Hasswnbusch et al., 1995	0/26	0/26	0/26	0/26	0/26	0/26	0/26	0/26
Cioni et al., 1995	0/10	0/10	0/10	0/10	0/10	0/10	1/25	0/10
DeLa Porte and VandeKelft, 1993	0/64	0/64	0/64	6/64	0/64	0/64	0/64	8/64
Probst, 1990	0/92	0/92	0/92	0/92	7/92	0/92	0/92	0/92
Kumar et al., 1997	0/12	0/12	0/12	2/12	2/12	0/12	0/12	0/12
Waisbrod and Gerbershagen, 1985	0/16	0/16	0/16	0/16	0/16	0/16	0/16	0/16

Total	20/1924	3/1924	3/1924	79/1924	64/1924	1/1924	12/1984	28/1538
%	1.03	.15	.15	4.1	3.32	.05	.6	1.8

Table 1B: This table shows the number of occurrences over the total number of implants for each of the studies cited. \*This paper is a review of 39 articles the numbers in this row are the average percentages of each occurrence over the total number of studies. Note: Citations cover both IPG and RF Systems

# IPG SPECIAL CONTROLS FOR IDENTIFIED RISK

## TABLE 1C

1

IDENTIFIED RISK	Potential Labeling Controls	Potential Consensus Standards Controls	Potential Guidance Documents Controls
A) LEAD MIGRATION	<ul style="list-style-type: none"> <li>Identify lead migration as possible adverse event</li> <li>Directions to secure lead with anchors in Physician's Manual</li> </ul>	<ul style="list-style-type: none"> <li>EN 1441 Medical Device Risk Analysis</li> </ul>	<ul style="list-style-type: none"> <li>Design Control Guidance for Medical Device Manufacturers</li> <li>Medical Device Labeling Suggested Format and Content</li> </ul>
B) INFECTION	<ul style="list-style-type: none"> <li>Identify infection as possible adverse event</li> </ul>	<ul style="list-style-type: none"> <li>Sterilization validation per AAMI/ISO 11135</li> <li>Sterilization validation per EN 556</li> <li>Sterile labeled medical devices EN 556</li> <li>EN 45501-1 subset has EN 861-1 "Packaging materials and systems for Medical Devices which are to be sterilized"</li> <li>EN 1441 Medical Device Risk Analysis</li> </ul>	<ul style="list-style-type: none"> <li>510(k) Sterility Review Guidance</li> <li>Medical Device Labeling Suggested Format and Content</li> </ul>
B) EPIDURAL HEMORRHAGE	<ul style="list-style-type: none"> <li>Identify epidural hemorrhage as possible adverse event</li> <li>Directions for needle insertion in Physician Manual</li> </ul>	<ul style="list-style-type: none"> <li>EN 1441 Medical Device Risk Analysis</li> </ul>	<ul style="list-style-type: none"> <li>Medical Device Labeling Suggested Format and Content</li> </ul>
B) SEROMA	<ul style="list-style-type: none"> <li>Identify seroma as possible adverse event</li> </ul>	<ul style="list-style-type: none"> <li>EN 1441 Medical Device Risk Analysis</li> </ul>	<ul style="list-style-type: none"> <li>Medical Device Labeling Suggested Format and Content</li> </ul>
B) HEMATOMA	<ul style="list-style-type: none"> <li>Identify Hematoma as possible adverse event</li> <li>Directions for implantation technique in Physician Manual</li> </ul>	<ul style="list-style-type: none"> <li>EN 1441 Medical Device Risk Analysis</li> </ul>	<ul style="list-style-type: none"> <li>Medical Device Labeling Suggested Format and Content</li> </ul>

NOTE : RECOMMENDED SPECIAL CONTROLS IN BOLD PRINT

# IPG SPECIAL CONTROLS FOR IDENTIFIED RISK

## TABLE 1C

2

IDENTIFIED RISK	Potential Labeling Controls	Potential Consensus Standards Controls	Potential Guidance Documents Controls
B) PARALYSIS	<ul style="list-style-type: none"> <li>Identify paralysis as possible adverse event</li> <li>Directions for needle insertion in Physician Manual</li> <li>Directions for implantation in Physician Manual</li> <li>Patient size selection guidance in Physicians manual</li> <li>Identify infection as possible adverse event</li> </ul>	<ul style="list-style-type: none"> <li>EN 1441 Medical Device Risk Analysis</li> </ul>	<ul style="list-style-type: none"> <li>Medical Device Labeling Suggested Format and Content</li> </ul>
C) CSF LEAKAGE	<ul style="list-style-type: none"> <li>Identify CSF leakage as possible adverse event</li> <li>Directions for implantation and insertion technique in Physician Manual</li> </ul>	<ul style="list-style-type: none"> <li>EN 1441 Medical Device Risk Analysis</li> </ul>	<ul style="list-style-type: none"> <li>Medical Device Labeling Suggested Format and Content</li> </ul>
D) UNDESIRABLE CHANGES IN STIMULATION <ul style="list-style-type: none"> <li>Intermittent Stimulation</li> <li>Over Stimulation</li> <li>Shock</li> </ul>	<ul style="list-style-type: none"> <li>Identify undesirable changes in stimulation as possible adverse event</li> <li>Warning regarding Anti-Theft Devices</li> <li>Cautions regarding effects of postural changes</li> </ul>	<ul style="list-style-type: none"> <li>EN/IEC-60601 series</li> <li>EN 1441 Medical Device Risk Analysis</li> <li>EN 45502-1 Active Implantable Medical Device -General Requirements for Safety, Marking ...</li> <li>ANSI/AAMI NS14 -1995 Implantable Spinal Cord Stimulators</li> </ul>	<ul style="list-style-type: none"> <li>FDA letter to industry "Important Information on Anti-Theft and Metal Detector Systems....Spinalcord Stimulators", Sept 28, 1998</li> <li>Guidance for Content of Premarket Submissions for Software Contained in Medical Devices</li> <li>General Principals of Software Validation</li> </ul>
E) PAIN AT THE IMPLANT SITE	<ul style="list-style-type: none"> <li>Identify implant site pain as possible adverse event</li> <li>Directions for needle insertion in Physician Manual</li> </ul>	<ul style="list-style-type: none"> <li>EN 1441 Medical Device Risk Analysis</li> </ul>	<ul style="list-style-type: none"> <li>Medical Device Labeling Suggested Format and Content</li> </ul>

NOTE : RECOMMENDED SPECIAL CONTROLS IN BOLD PRINT

**IPG SPECIAL CONTROLS FOR IDENTIFIED RISK**  
**TABLE 1C**

3

IDENTIFIED RISK	Potential Labeling Controls	Potential Consensus Standards Controls	Potential Guidance Documents Controls
F) ALLERGIC OR REJECTION RESPONSE TO IMPLANTED MATERIALS	<ul style="list-style-type: none"> <li>Identify immune response as possible adverse event</li> </ul>	<ul style="list-style-type: none"> <li>EN ISO 10993-1 Biological Evaluation of Medical Devices - Part 1</li> <li>EN 1441 Medical Device Risk Analysis</li> </ul>	<ul style="list-style-type: none"> <li>Medical Device Labeling Suggested Format and Content</li> </ul>
G) LOCAL SKIN EROSION	<ul style="list-style-type: none"> <li>Identify skin erosion response as possible adverse event</li> <li>Directions for implantation in Physician Manual</li> <li>Patient size selection guidance in Physician manual</li> </ul>	<ul style="list-style-type: none"> <li>EN 1441 Medical Device Risk Analysis</li> </ul>	<ul style="list-style-type: none"> <li>Medical Device Labeling Suggested Format and Content</li> </ul>
H) DEVICE FAILURE <ul style="list-style-type: none"> <li>Lead Breakage</li> <li>Hardware Malfunction</li> <li>Loose Connection</li> </ul>		<ul style="list-style-type: none"> <li>ANSI/AAMI NS14 -1995 Implantable Spinal Cord Stimulators</li> <li>EN 45502-1 Active Implantable Medical Device -General Requirements for Safety, Marking ...</li> </ul>	<ul style="list-style-type: none"> <li>Design Control Guidance for Medical Devices</li> <li>Guidance for Content of Premarket Submissions for Software Contained in Medical Devices</li> <li>General Principles of Software Validation</li> </ul>
I) OTHER <ul style="list-style-type: none"> <li>Psychosis</li> </ul>	<ul style="list-style-type: none"> <li>Recommend patients have Psychological Screening prior to implant in Physician Manual</li> <li>Contraindications: Patients are contraindicated for internalization if they are clearly unsuccessful during screening procedure, or if they are unable to properly operate the system</li> </ul>		
J) BATTERY FAILURE	<ul style="list-style-type: none"> <li>Disclose expected battery life in patient &amp; Physician Manuals</li> </ul>	<ul style="list-style-type: none"> <li>EN 1441 Medical Device Risk Analysis</li> </ul>	<ul style="list-style-type: none"> <li>Medical Device Labeling Suggested Format and Content</li> <li>Design Control Guidance for Medical Devices</li> </ul>

NOTE : RECOMMENDED SPECIAL CONTROLS IN BOLD PRINT

TABLE 2

## MDR REPORTS

Event Category	Total Set Count	Total Set %	Last 5 ¼ Count	Last 5 ¼ %	1998 Count	1998 %
A) Lead Migration	1	0.25%	1	0.51%	0	0.00%
B) Infection	14	3.43%	14	7.07%	3	12.50%
Epidural Hemorrhage	0	0.00%	0	0.00%	0	0.00%
Seroma	1	0.25%	1	0.51%	1	4.17%
Hematoma	0	0.00%	0	0.00%	0	0.00%
Paralysis	0	0.00%	0	0.00%	0	0.00%
C) CSF Leak	0	0.00%	0	0.00%	0	0.00%
D) Intermittent Stimulation	50	12.25%	21	10.61%	0	0.00%
Over Stimulation	33	8.09%	18	9.09%	4	16.67%
Shock	23	5.64%	18	9.09%	0	0.00%
E) Pain at Implant Site	10	2.45%	6	3.03%	0	0.00%
F) Allergic Reaction	1	0.25%	1	0.51%	1	4.17%
G) Skin Erosion	2	0.49%	2	1.01%	2	8.33%
H) Lead Breakage	15	3.68%	11	5.56%	1	4.17%
Hardware Malfunction	44	10.78%	16	8.08%	1	4.17%
Loose Connection	4	0.98%	1	0.51%	0	0.00%
I) Other	144	35.29%	80	40.40%	11	45.83%
J) Battery Failure	66	16.18%	8	4.04%	0	0.00%
Total	408	100.00%	198	100.00%	24	100.00%

Table 2: This table shows the number of incidents reported as MDR's during the period from 1984 to March 22, 1999, with the exception of 1991.

SUPPLEMENTAL DATA SHEET

FORM APPROVED: OMB NO. 3210-0138  
EXPIRATION DATE: January 1, 2000  
(See OMB Statement on Page 2)

1. GENERIC TYPE OF DEVICE

STIMULATOR, SPINAL CORD, TOTALLY IMPLANTED FOR PAIN RELIEF

2. ADVISORY PANEL

NEUROLOGICAL DEVICES PANEL

3. IS DEVICE AN IMPLANT?

☒ Yes ☐ No

4. INDICATIONS FOR USE PRESCRIBED, RECOMMENDED, OR SUGGESTED IN THE DEVICE'S LABELING THAT WERE CONSIDERED BY THE ADVISORY  
TOTALLY IMPLANTED SPINAL CORD STIMULATORS FOR PAIN RELIEF ARE INDICATED FOR THE  
TREATMENT OF CHRONIC INTRACTABLE PAIN OF THE TRUNK AND LIMBS

5. IDENTIFICATION OF ANY RISKS TO HEALTH PRESENTED BY DEVICE

General LEAD MIGRATION, INFECTION, EPIDURAL HEMORRHAGE, SEROMA, HEMATOMA,  
PARALYSIS, CSF LEAKAGE, UNDESIRABLE CHANGES IN STIMULATION, PAIN AT RECEIVER  
SITE, ALLERGIC RESPONSE, SKIN EROSION, DEVICE FAILURE, BATTERY FAILURE

Specific Hazards to Health

- a. INFECTION
- b. LEAD MIGRATION
- c. SEROMA AT IPG SITE
- d. OTHERS

Characteristics or Features of Device Associated with Hazard

- a. SURGICAL TECHNIQUE/CARE
- b. INADEQUATE LEAD ANCHORING
- c. SURGICAL TECHNIQUE
- d. SURGICAL TECHNIQUE

6. RECOMMENDED ADVISORY PANEL CLASSIFICATION AND PRIORITY

Classification CLASS II

Priority (Class II or III Only)

7. IF DEVICE IS AN IMPLANT, OR IS LIFE-SUSTAINING OR LIFE-SUPPORTING AND HAS BEEN CLASSIFIED IN A CATEGORY OTHER THAN CLASS III, EXPLAIN FULLY, THE REASONS FOR THE LOWER CLASSIFICATION WITH SUPPORTING DOCUMENTATION AND DATA

RF SYSTEMS WITH EXTERNAL POWER SOURCES ARE CLASS II. THESE SYSTEMS ARE  
DEFINED IN 882.5880 OF THE CFR.

8. SUMMARY OF INFORMATION, INCLUDING CLINICAL EXPERIENCE OR JUDGMENT, UPON WHICH CLASSIFICATION RECOMMENDATION IS BASED

1. OVER 10 YEARS OF CLINICAL USE DEMONSTRATING THE DEVICE IS SAFE AND EFFECTIVE
2. SPECIAL CONTROLS AND GENERAL CONTROLS ARE AVAILABLE TO REASONABLY ASSURE  
THE DEVICE'S SAFETY AND EFFECTIVENESS
3. RISK ASSOCIATED WITH TOTALLY IMPLANTED DEVICE ARE SIMILAR TO STIMULATORS  
USED FOR THE SAME INDICATION WHICH ARE CLASS II

9. IDENTIFICATION OF ANY NEEDED RESTRICTIONS ON THE USE OF THE DEVICE

10. IF DEVICE IS IN CLASS I, RECOMMEND WHETHER FDA SHOULD EXEMPT IT FROM

Justification / Comments

☐ a. Registration / Device Listing

☐ b. Premarket Notification

☐ c. Records and Reports

☐ d. Good Manufacturing Practice

11. EXISTING STANDARDS APPLICABLE TO THE DEVICE, DEVICE SUBASSEMBLIES (Components) OR DEVICE MATERIALS (Parts and Accessories)

- ANSI/AMMI NS14-1995 STANDARD "IMPLANTABLE SPINAL CORD STIMULATORS"

- EN 45502-1 ACTIVE IMPLANTABLE MEDICAL DEVICE-GENERAL REQUIREMENTS FOR  
SAFETY, MARKING ...

- SEE SPECIAL CONTROLS CHART FOR ADDITIONAL STANDARDS

12. COMPLETE THIS FORM PURSUANT TO 21 CFR PART 860 AND SUBMIT TO:

Food and Drug Administration  
Center for Devices and Radiological Health  
Office of Health and Industry Programs (HFZ-215)  
1350 Piccard Drive  
Rockville, MD 20850

### OMB STATEMENT

Public reporting burden for this collection of information is estimated to average 1-2 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Officer, Paperwork Reduction Project (0910-0138)  
Hubert H. Humphrey Building, Room 531-H  
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Washington, DC 20201

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE — FOOD AND DRUG ADMINISTRATION <b>GENERAL DEVICE CLASSIFICATION QUESTIONNAIRE</b>		FORM APPROVED: OMB NO. 0910-0138 EXPIRATION DATE: January 1, 2000 (See OMB Statement on Page 2)
PANEL MEMBER / PETITIONER <b>ADVANCED NEUROMODULATION SYSTEMS, INC.</b>		DATE <b>5/20/99</b>
GENERIC TYPE OF DEVICE <b>STIMULATOR, SPINAL-CORD, TOTALLY IMPLANTED FOR PAIN RELIEF</b>	CLASSIFICATION RECOMMENDATION <b>CLASS II</b>	
1. IS THE DEVICE LIFE-SUSTAINING OR LIFE-SUPPORTING ?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	Go to Item 2.
2. IS THE DEVICE FOR A USE WHICH IS OF SUBSTANTIAL IMPORTANCE IN PREVENTING IMPAIRMENT OF HUMAN HEALTH ?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	Go to Item 3.
3. DOES THE DEVICE PRESENT A POTENTIAL UNREASONABLE RISK OF ILLNESS OR INJURY ?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	Go to Item 4.
4. DID YOU ANSWER "YES" TO ANY OF THE ABOVE 3 QUESTIONS ?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	If "Yes," go to Item 7. If "No," go to Item 5.
5. IS THERE SUFFICIENT INFORMATION TO DETERMINE THAT GENERAL CONTROLS ARE SUFFICIENT TO PROVIDE REASONABLE ASSURANCE OF SAFETY AND EFFECTIVENESS ?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	If "Yes," Classify in Class I. If "No," go to Item 6.
6. IS THERE SUFFICIENT INFORMATION TO ESTABLISH SPECIAL CONTROLS TO PROVIDE REASONABLE ASSURANCE OF SAFETY AND EFFECTIVENESS ?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	If "Yes," go to Item 7. If "No," Classify in Class I.
7. IS THERE SUFFICIENT INFORMATION TO ESTABLISH SPECIAL CONTROLS TO PROVIDE REASONABLE ASSURANCE OF SAFETY AND EFFECTIVENESS ? IF YES, CHECK THE SPECIAL CONTROL(S) NEEDED TO PROVIDE SUCH REASONABLE ASSURANCE. FOR CLASS II.	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	If "Yes," Classify in Class II If "No," Classify in Class III
<div style="display: flex; justify-content: space-between;"> <div style="width: 60%;"> <input checked="" type="checkbox"/> Postmarket Surveillance  <input checked="" type="checkbox"/> Performance Standard(s)  <input type="checkbox"/> Patient Registries  <input type="checkbox"/> Device Tracking  <input checked="" type="checkbox"/> Testing Guidelines  <input checked="" type="checkbox"/> Other (specify)  <u>LABELING</u>        </div> <div style="width: 35%;"></div> </div>		
8. IF A REGULATORY PERFORMANCE STANDARD IS NEEDED TO PROVIDE REASONABLE ASSURANCE OF THE SAFETY AND EFFECTIVENESS OF A CLASS II OR III DEVICE, IDENTIFY THE PRIORITY FOR ESTABLISHING SUCH A STANDARD.		
<input checked="" type="checkbox"/> Low Priority _____ <input type="checkbox"/> Medium Priority _____ <input type="checkbox"/> High Priority _____ <input type="checkbox"/> Not Applicable _____		
9. FOR A DEVICE RECOMMENDED FOR RECLASSIFICATION INTO CLASS II, SHOULD THE RECOMMENDED REGULATORY PERFORMANCE STANDARD BE IN PLACE BEFORE THE RECLASSIFICATION TAKES EFFECT ?	<input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NOT Applicable	
10. FOR A DEVICE RECOMMENDED FOR CLASSIFICATION / RECLASSIFICATION INTO CLASS III, IDENTIFY THE PRIORITY FOR REQUIRING PREMARKET APPROVAL APPLICATION (PMA) SUBMISSIONS.		
<input type="checkbox"/> Low Priority _____ <input type="checkbox"/> Medium Priority _____ <input type="checkbox"/> High Priority _____ <input type="checkbox"/> Not Applicable _____		

<b>1a. CAN THERE OTHERWISE BE REASONABLE ASSURANCE OF ITS SAFETY AND EFFECTIVENESS WITHOUT RESTRICTIONS ON ITS SALE, DISTRIBUTION OR USE, BECAUSE OF ANY POTENTIALITY FOR HARMFUL EFFECT OR THE COLLATERAL MEASURES NECESSARY FOR THE DEVICE'S USE?</b>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	If "Yes," go to Item 12. If "No," go to Item 11b.
<b>1b. IDENTIFY THE NEEDED RESTRICTION(S) (If Item 11a. was checked "NO.")</b> <input type="checkbox"/> Only upon the written or oral authorization of a practitioner licensed by law to administer or use the device <input type="checkbox"/> Use only by persons with specific training or experience in its use <input type="checkbox"/> Use only in certain facilities <input checked="" type="checkbox"/> Other (Specify) <u>PREScription DEVICE</u> <u>LABELING REQUIREMENT</u>		
<b>12. COMPLETE THIS FORM PURSUANT TO 2: CFR PART 860 AND SUBMIT TO:</b> Food and Drug Administration Center for Devices and Radiological Health Office of Health and Industry Programs (HFZ-215) 1350 Piccard Drive Rockville, MD 20850		

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EUROPEAN STANDARD

EN 45502-1

NORME EUROPÉENNE

EUROPÄISCHE NORM

August 1997

ICS 11.040.01

Descriptors: Medical equipment, surgical implants, safety requirements, accident prevention, specifications, protection, tests, technical notices, information, packing, sterility, marking...

English version

## Active implantable medical devices — Part 1: General requirements for safety, marking and information to be provided by the manufacturer

Dispositifs médicaux implantables actifs —

Partie 1: Règles générales de sécurité, marquage et  
informations fournies par le fabricant

Aktive implantierbare medizinische Geräte —

Teil 1: Allgemeine Festlegungen für die Sicherheit,  
Aufschriften und vom Hersteller zur Verfügung zu  
stellende Informationen

This European Standard was approved by CENELEC on 11 March 1997 and by CEN on 1997-03-14.

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Ref. No. EN 45502-1 : 1997 E

## Introduction

This standard specifies general requirements for ACTIVE IMPLANTABLE MEDICAL DEVICES, to provide basic assurance of safety for both patients and users.

To minimize the likelihood of a device being misused, this standard also details comprehensive requirements for MARKINGS and for other information to be supplied as part of the documentation with any ACTIVE IMPLANTABLE MEDICAL DEVICE.

For particular types of ACTIVE IMPLANTABLE MEDICAL DEVICE, the general requirements are supplemented or modified by the requirements of particular standards which are in preparation<sup>1)</sup> as separate Parts of EN 45502. A requirement of such a particular standard takes priority over the corresponding requirement of this general standard. Where particular standards exist, this general standard should not be used alone. Special care is required when applying this general standard alone to ACTIVE IMPLANTABLE MEDICAL DEVICES for which no particular standard has yet been published.

## 1 Scope

This Part 1 of EN 45502 specifies requirements that are generally applicable to ACTIVE IMPLANTABLE MEDICAL DEVICES. For particular types of ACTIVE IMPLANTABLE MEDICAL DEVICES, these essential requirements are supplemented or modified by the requirements of particular standards which form additional parts of this European Standard.

The tests that are specified in EN 45502 are type tests and are to be carried out on samples of a device to show compliance.

This Part of EN 45502 is applicable not only to ACTIVE IMPLANTABLE MEDICAL DEVICES that are electrically powered but also to those powered by other energy sources (for example by gas pressure or by springs).

This Part of EN 45502 is also applicable to some non-implantable parts and accessories of the devices (see note 1).

NOTE 1. The device that is commonly referred to as an ACTIVE IMPLANTABLE MEDICAL DEVICE may in fact be a single device, a combination of devices, or a combination of a device or devices and one or more accessories. Not all of these parts are required to be either partially or totally implantable, but there is a need to specify some requirements of non-implantable parts and accessories if they could affect the safety or performance of the implantable device.

NOTE 2. The terminology used in this European Standard is intended to be consistent with the terminology of Directive 90/385/EEC.

NOTE 3. In this European Standard, terms printed in SMALL CAPITAL LETTERS are used as defined in clause 3. Where a defined term is used as a qualifier in another term, it is not printed in small capital letters unless the concept thus qualified is also defined.

## 2 Normative references

This European Standard incorporates by dated or undated reference provisions from other publications. These normative references are cited at the appropriate places in the text and the publications are listed hereafter. For dated references, subsequent amendments to or revisions of any of these publications apply to this European Standard only when incorporated in it by amendment or revision. For undated references the latest edition of the publication referred to applies.

- |                      |  |
|----------------------|--|
| EN 540 : 1993        | <i>Clinical investigation of medical devices for human subjects</i>  |
| EN 556 : 1994        | <i>Sterilization of medical devices — Requirements for medical devices to be labelled 'sterile'</i>  |
| EN 868-1 : 1997      | <i>Packaging materials for sterilization of wrapped goods</i><br><i>Part 1: General requirements and requirements for the validation of packaging for terminally-sterilized devices</i>  |
| EN 980 : 1996        | <i>Terminology, symbols and information provided with medical devices — Graphical symbols for use in the labelling of medical devices</i>  |
| EN 60068-2-32 : 1993 | <i>Environmental testing</i><br><i>Part 2: Tests — Test Ed: Free fall</i><br>(IEC 60068-2-32 : 1975 + A2 : 1990)   |
| EN 60068-2-47 : 1993 | <i>Environmental testing</i><br><i>Part 2: Tests — Mounting of components, equipment and other articles for dynamic tests including shock (Ea), bump (Eb), vibration (Fc and Fd) and steady state acceleration (Ga) and guidance</i><br>(IEC 68-2-47 : 1982) |
| EN 60601-1 : 1990    | <i>Medical electrical equipment</i><br><i>Part 1: General requirements for safety</i><br>(IEC 601-1 : 1988)  |
| EN 60601-1-1 : 1993  | <i>Medical electrical equipment</i><br><i>Part 1: General requirements for safety 1. Collateral Standard: Safety requirements for medical electrical systems</i><br>(IEC 601-1-1 : 1992)   |

<sup>1)</sup> At present (July 1997) particular standards for implantable cardiac pulse generators, implantable cardiac defibrillators, implantable infusion pumps, implantable neurostimulators and cochlear implants are in preparation.

### 3.12 sealed source

A source containing RADIOACTIVE SUBSTANCES firmly incorporated in solid and effectively inactive materials, or sealed in an inactive container of sufficient strength to prevent, under normal conditions of use, any dispersion of RADIOACTIVE SUBSTANCES.

[Based on 80/836/Euratom]

### 3.13 medicinal substance

Substance which, when used separately, is intended for the treatment or prevention of disease in human beings, or which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings.

[Based on Article 1 of Directive 65/65/EEC]

### 3.14 harm

Physical injury or damage to health or property.

### 3.15 hazard

A potential source of HARM.

### 3.16 unacceptable hazard

HAZARD where the probability of it causing HARM is greater than a stated value determined by considering the severity of the HARM.

### 3.17 hazard control

A design feature of an ACTIVE IMPLANTABLE MEDICAL DEVICE intended to ensure that it does not cause an UNACCEPTABLE HAZARD.

### 3.18 portable (equipment)

(Equipment) intended to be moved from one location to another while being used or between periods of use while being carried by one or more persons.

### 3.19 hand held (equipment)

(Equipment) intended to be supported by the hand during normal use.

## 4 Symbols and abbreviations (optional)

NOTE. Requirements may be included in this clause in subsequent Parts of EN 45502. There are no requirements specified in this Part of EN 45502. However this does not preclude the use of symbols defined in other standards nor special symbols defined in the accompanying documentation.

## 5 General requirements for non-implantable parts

5.1 The non-implantable part of an ACTIVE IMPLANTABLE MEDICAL DEVICE which is connected to or equipped with a power source shall comply with the requirements of EN 60601-1, EN 60601-1-1, EN 60601-1-2 and EN 60601-1-4, unless a requirement in these standards is superseded by a requirement in this Part of EN 45502.

### 5.2 (Vacant)

NOTE. Requirements may be included in this clause in subsequent Parts of EN 45502.

### 6 (Vacant)

NOTE. Requirements may be included in this clause in subsequent Parts of EN 45502. There are no requirements specified in this Part of EN 45502.

## 7 General arrangement of the packaging

7.1 Implantable parts of ACTIVE IMPLANTABLE MEDICAL DEVICES shall be supplied in a NON-REUSABLE PACK (see 14.1).

NOTE. The NON-REUSABLE PACK is designed to be sealed yet allow its contents to be sterilized by the manufacturer.

Compliance shall be checked by inspection.

7.2 The NON-REUSABLE PACK shall be enclosed in the SALES PACKAGING.

Compliance shall be checked by inspection.

## 8 General markings for active implantable medical devices

NOTE. Any MARKING required by this Part of EN 45502, in either figures or letters, may be expressed using appropriate symbols specified in relevant European Standards, e.g. EN 980. (See also clauses 9, 11 and 13.)

8.1 Any warning notices required by this European Standard shall be prominently displayed.

Compliance shall be checked by inspection.

8.2 Implanted parts of devices and components of those parts shall be identified in such a way as to allow any necessary measure to be taken following the discovery of a possible HAZARD in connection with any implanted part.

Compliance shall be checked by review of the manufacturer's explanation of the relationship between the identity of the ACTIVE IMPLANTABLE MEDICAL DEVICE and the identities of its component parts.

## 9 Markings on the sales packaging

NOTE. The SALES PACKAGING may be required to carry other regulatory markings, such as the CE mark of conformity and identification of the notified body authorizing the mark.

9.1 If the SALES PACKAGING contains any RADIOACTIVE SUBSTANCE, it shall have MARKINGS that state the type and activity of the RADIOACTIVE SUBSTANCE.

Compliance shall be checked by inspection.

9.2 The SALES PACKAGING shall bear the name and address of the manufacturer, the address including at least the city and the country.

Compliance shall be checked by inspection.

### 11.3 The symbol

STERILE

shall be prominently displayed on the STERILE PACK (see EN 980).

Compliance shall be checked by inspection.

11.4 The STERILE PACK shall bear the year and month when the packaged device was manufactured, as required by 9.6.

Compliance shall be checked by inspection.

11.5 The STERILE PACK shall bear the 'use before' date, as required by 9.7.

Compliance shall be checked by inspection.

11.6 The STERILE PACK shall bear a description of the device, as required by 9.3.

Compliance shall be checked by inspection.

11.7 The MARKINGS on the STERILE PACK shall identify the contents, unless the STERILE PACK is transparent and the contents are visible.

Compliance shall be checked by inspection.

11.8 If the intended use of a device enclosed in a STERILE PACK requires that it be connected to other devices or accessories not included in the STERILE PACK, the STERILE PACK shall identify the connector types or configurations, as required by 9.9.

Compliance shall be checked by inspection.

11.9 The STERILE PACK shall bear instructions for opening the package.

Compliance shall be checked by inspection.

### 12 Construction of the non-reusable pack

12.1 The NON-REUSABLE PACK shall comply with EN 868-1.

Compliance shall be checked by inspection and by review of records provided by the manufacturer.

12.2 The NON-REUSABLE PACK shall be so designed that once it has been opened, this is readily apparent and, if it has been opened and resealed, it shall remain thereafter apparent that it has been previously opened.

Compliance shall be checked by inspection.

12.3 The markings on the NON-REUSABLE PACK shall be indelible.

Compliance shall be confirmed as described in 10.3.

### 13 Markings on the active implantable medical device

13.1 As far as practicable and appropriate, the ACTIVE IMPLANTABLE MEDICAL DEVICE shall bear the name or trademark of the manufacturer, the model designation of the device and, if applicable, the batch number or serial number of the device.

Compliance shall be checked by inspection, and by a wet rub test.

Wet rub test: The MARKINGS shall be rubbed by hand, without undue pressure, first for 15<sup>s</sup><sub>0</sub> s with a cloth rag soaked in methylated spirit at ambient temperature and then for 15<sup>s</sup><sub>0</sub> s with a cloth rag soaked in water at ambient temperature after which the MARKINGS shall remain clearly legible.

13.2 If the individual implantable units of a particular model of ACTIVE IMPLANTABLE MEDICAL DEVICE incorporate different models of power source, it shall be possible to group the devices by power source, for example by reference to the accompanying documents or by use of a designating suffix.

Compliance shall be checked by inspection.

13.3 Implantable parts of an ACTIVE IMPLANTABLE MEDICAL DEVICE with an internal power source shall incorporate a code by which the device and the manufacturer can be unequivocally identified (particularly with regard to the model of device and year of manufacture). It shall be possible to read this code, when necessary, without knowledge of the make or model of device and without the need for a surgical operation.

Compliance shall be confirmed by the procedure defined by the manufacturer in the instructions for use (see 28.6).

13.4 Any visual indicators carried on an ACTIVE IMPLANTABLE MEDICAL DEVICE shall be understandable with reference to the accompanying documentation, taking account of the training and knowledge of the likely user.

Compliance shall be checked by inspection.

### 14 Protection from unintentional biological effects being caused by the active implantable medical device

14.1 Any implantable part of an ACTIVE IMPLANTABLE MEDICAL DEVICE or other parts enclosed in the NON-REUSABLE PACK (see 7.1) and not contained within an implantable, hermetically-sealed, impermeable container shall be sterile in conformity with EN 556.

Compliance shall be confirmed if the process validation records provided by the manufacturer establish that the non-reusable pack has been sterilized by a validated process (for example, according to EN 550, EN 552, or EN 554).

14.2 Any part of the ACTIVE IMPLANTABLE MEDICAL DEVICE, intended in normal use to be in contact with body fluids, shall cause no unacceptable release of particulate matter when the device is used as intended by the manufacturer.

## 17 Protection from harm to the patient caused by heat

17.1 No outer surface of an implantable part of the ACTIVE IMPLANTABLE MEDICAL DEVICE shall be greater than 2 °C above the normal surrounding body temperature of 37 °C when implanted, and when the ACTIVE IMPLANTABLE MEDICAL DEVICE is in normal operation or in any single-fault condition (see 19.3).

Compliance shall be confirmed by inspection of a design analysis provided by the manufacturer, supported by the manufacturer's calculations and data from test studies as appropriate.

### 17.2 (Vacant.)

NOTE. Requirements may be included in this clause in subsequent Parts of EN 45502.

## 18 Protection from ionizing radiation released or emitted from the active implantable medical device

18.1 If an ACTIVE IMPLANTABLE MEDICAL DEVICE contains any RADIOACTIVE SUBSTANCE, it shall be in the form of a sealed source.

Compliance shall be confirmed by inspection of a design analysis provided by the manufacturer, supported by data from test studies as appropriate.

18.2 If an ACTIVE IMPLANTABLE MEDICAL DEVICE contains any RADIOACTIVE SUBSTANCES, consequent exposure to ionizing radiation shall be justified by the advantages which the RADIOACTIVE SUBSTANCES provide.

Compliance shall be confirmed by inspection of the manufacturer's calculations and data from test studies as appropriate.

18.3 If an ACTIVE IMPLANTABLE MEDICAL DEVICE contains any RADIOACTIVE SUBSTANCES, consequent exposure to ionizing radiation shall be kept as low as reasonably achievable.

Compliance shall be confirmed by inspection of a design analysis provided by the manufacturer, supported by the manufacturer's calculations and data from test studies as appropriate.

## 19 Protection from unintended effects caused by the device

NOTE. See also 28.20.

19.1 Implantable parts of an ACTIVE IMPLANTABLE MEDICAL DEVICE shall be designed so that any gradual, long term change that might occur within the lifetime of the device is not an UNACCEPTABLE HAZARD.

Compliance shall be confirmed if records provided by the manufacturer establish that no HARM will result from ageing of the device:

- a) by analogy with published data; or
- b) by the selection of materials already shown to be stable by proven clinical use in a similar application; or
- c) by experience with similar devices already on the market together with evidence of traceability to the materials used in those devices; or
- d) by compliance with published procedures for evaluation of materials for implantation.

19.2 If the implantable part of an ACTIVE IMPLANTABLE MEDICAL DEVICE contains within it a source of power, such as a battery or a pressure reservoir, the ACTIVE IMPLANTABLE MEDICAL DEVICE shall include an 'elective replacement indicator' that gives advance warning of energy source depletion causing the 'end-of-life' of the device. The manufacturer shall define the interval between the activation of this elective replacement indicator and the end-of-life of the device.

Compliance shall be confirmed by inspection of a design analysis provided by the manufacturer, supported by the manufacturer's calculations and data from test studies as appropriate.

19.3 An ACTIVE IMPLANTABLE MEDICAL DEVICE shall be designed so that the failure of any single component, part or (if the device incorporates a programmable electronic system) software program shall not cause an UNACCEPTABLE HAZARD.

Assessment. The HAZARDS caused by possible single fault conditions and associated with each function of the device shall be identified. For each HAZARD, the probability of HARM shall be assessed by a design analysis that takes account of any HAZARD CONTROL and allows the probability of HARM being caused by each fault condition to be evaluated. The design analysis shall be supported by test studies as appropriate.

For each HAZARD, the HAZARD CONTROLS incorporated in the device and the assessment of probability of HARM shall be documented, together with the design analysis and appropriate test results.

Compliance shall be confirmed by review of the appropriate documentation prepared by the manufacturer.

19.4 Possible side effects arising from the intended use of an ACTIVE IMPLANTABLE MEDICAL DEVICE shall not cause undue HARM.

Assessment. Side effects and benefits from the intended use of the device shall be identified either by reference to current medical practice and demonstrated by analogy, or by reference to clinical investigations conducted according to EN 540.

Compliance shall be confirmed by an assessment of the manufacturer's documentation.

## 21 Protection of the device from changes caused by high power electrical fields applied directly to the patient

NOTE. See also 28.12, 28.13.

21.1 Implanted electrically-conductive parts (of an ACTIVE IMPLANTABLE MEDICAL DEVICE) in contact with the body shall be constructed so that effects caused by high power electrical treatment applied directly to the patient (for example, application of diathermy) will not damage the device, provided that the implanted parts neither lie directly in the applied current path nor lie within the part of the body being treated.

Compliance shall be confirmed by inspection of a design analysis provided by the manufacturer, supported by data and calculations from test studies as appropriate.

### 21.2 (Vacant)

NOTE. Requirements may be included in this clause in subsequent Parts of EN 45502.

## 22 Protection of the active implantable medical device from changes caused by miscellaneous medical treatments

NOTE. See also 28.12, 28.14 and 28.15.

22.1 The implantable parts of an ACTIVE IMPLANTABLE MEDICAL DEVICE shall be designed and constructed so that no irreversible change will be caused by exposure to diagnostic levels of ultrasonic energy.

Test. The implantable parts of the ACTIVE IMPLANTABLE MEDICAL DEVICE, other than LEADS or CATHETERS, shall be immersed in a water bath at room temperature and subjected for one hour to ultrasonic energy of  $500 \text{ W/m}^2 \pm 5\%$  when using a spatial peak, temporal average mode. The signal used shall be pulsed with a duty cycle of  $50\% \pm 10\%$ . The frequency selected shall be between 2 MHz and 5 MHz.

NOTE. This test is not applied to LEADS and CATHETERS as it is presumed these devices will not be affected by diagnostic ultrasound.

Compliance shall be confirmed by checking that no irreversible damage is caused by the test by inspection of documentation provided by the manufacturer, supported by data from test studies as appropriate.

### 22.2 (Vacant)

NOTE. Requirements may be included in this clause in subsequent Parts of EN 45502.

## 23 Protection of the active implantable medical device from mechanical forces

23.1 Parts of an ACTIVE IMPLANTABLE MEDICAL DEVICE that are either HAND-HELD in normal use or PORTABLE and weigh not more than 10 kg, shall be constructed so that shocks caused by mishandling or dropping while in use do not damage the device.

Test. HAND-HELD or PORTABLE parts of an ACTIVE IMPLANTABLE MEDICAL DEVICE weighing up to 10 kg shall withstand the free fall test in accordance with EN 60068-2-32 : Part 2 test Ed, under the following conditions:

a) test surface:

hard wood, density not less than  $630 \text{ kg/m}^3$ , thickness between 50 and 55 mm;

b) height of fall:

i) hand-held devices: 1 m;

ii) PORTABLE devices: 50 mm;

c) attitude from which specimen is dropped: attitude as in normal use.

Compliance shall be confirmed if the dropped part operates as stated in the manufacturer's original specification for that part when it is checked after performing the complete procedure above.

23.2 Implantable parts or patient-carried parts of an ACTIVE IMPLANTABLE MEDICAL DEVICE, other than LEADS or CATHETERS, shall be constructed to withstand the mechanical forces which may occur during normal conditions of use.

Test. Each implanted part or patient-carried part of an ACTIVE IMPLANTABLE MEDICAL DEVICE shall be mounted in accordance with the guidance given in appendix A to EN 60068-2-47 on test equipment capable of subjecting the device to a random vibration test in accordance with HD 323.2.36, test Fdb under the following conditions:

a) frequency range: 5 Hz — 150 Hz;

b) ASD spectrum level:  $0,1 \text{ g}^2/\text{Hz}$ ;

c) duration of conditioning: 90 min equally divided between three mutually perpendicular directions;

d) reproducibility: medium.

Compliance shall be confirmed if the ACTIVE IMPLANTABLE MEDICAL DEVICE conforms to the device specifications after performing the complete procedure above.

23.3 Implantable LEADS or CATHETERS shall withstand the tensile forces that might occur during or after implantation, without fracture of any conductor or cracking of either any functional electrical insulation or of the body of the LEAD or CATHETER.

Compliance shall be confirmed by review of a design analysis provided by the manufacturer supported by the manufacturer's calculations and data from test studies as appropriate.

23.4 Implantable LEADS having a junction of two or more conductive components shall be designed such that the junctions are relieved from strain caused by the flexural stresses that might occur during or after implantation.

Compliance shall be confirmed by inspection and, if necessary, by review of a design analysis provided by the manufacturer supported by the manufacturer's calculations and data from test studies as appropriate.

## 27 Protection of the active implantable medical device from electromagnetic non-ionizing radiation

27.1 Implantable parts of an ACTIVE IMPLANTABLE MEDICAL DEVICE shall not cause any HARM because of susceptibility to electrical influences due to external electro-magnetic fields, whether through malfunction of the device, damage to the device, heating of the device or by causing local increase of induced electrical current density within the patient.

Assessment. Possible HAZARDS shall be identified, taking into account the electro-magnetic environment in which the ACTIVE IMPLANTABLE MEDICAL DEVICE is intended to be used. For each HAZARD, the probability of HARM shall be evaluated through a design analysis that takes account of any HAZARD CONTROLS. The design analysis shall be supported by test studies as appropriate.

NOTE. As a first guide, consider a magnetic intensity of 150 A/m falling inversely with frequency above 100 kHz to a maximum test frequency of 30 MHz. The electric field need not be investigated.

Compliance shall be confirmed by review of the appropriate documentation prepared by the manufacturer.

### 27.2 (Vacant)

NOTE. Requirements may be included in this clause in subsequent Parts of EN 45502.

## 28 Accompanying documentation

NOTE. The accompanying documentation may be required to carry other regulatory markings, such as the CE mark of conformity and identification of the notified body authorizing the mark.

28.1 The accompanying documentation shall include the name and address of the manufacturer, the address including at least the city and the country.

Compliance shall be checked by inspection.

28.2 If the package contains any RADIOACTIVE SUBSTANCE, the accompanying documentation shall include information about the type and activity of the RADIOACTIVE SUBSTANCE. (See also clause 18.)

Compliance shall be checked by inspection.

28.3 The accompanying documentation shall include a description of the device (e.g. cardiac pulse generator) and the model designation.

Compliance shall be checked by inspection.

28.4 If the package contains an implantable part of an ACTIVE IMPLANTABLE MEDICAL DEVICE intended to be connected to another implantable device or implantable accessory, the accompanying documentation shall provide information on the maximum proven connector retention strength, determined according to 23.6.

Compliance shall be checked by inspection.

28.5 The accompanying documentation shall include information listing the accessories that might be required with the device and their essential functions. Compliance shall be checked by inspection.

28.6 The accompanying documentation shall include an explanation of the method of interpreting the identification code required by 13.3.

Compliance shall be checked by inspection.

28.7 If applicable, the accompanying documentation shall include information regarding the medicinal products which the ACTIVE IMPLANTABLE MEDICAL DEVICE is designed to administer. (See also 14.4.)

NOTE. This subclause does not apply to any MEDICINAL SUBSTANCE which forms an integral part of the ACTIVE IMPLANTABLE MEDICAL DEVICE.

Compliance shall be checked by inspection.

28.8 The accompanying documentation shall describe the intended use of the device, give the device specifications and characteristics, and provide any information about significant side effects (see 19.4).

Compliance shall be checked by inspection.

28.9 The accompanying documentation shall provide information allowing the physician to select a suitable device, its accessories and related devices (for example, a programmer).

Compliance shall be checked by inspection.

28.10 The accompanying documentation shall include instructions for using the ACTIVE IMPLANTABLE MEDICAL DEVICE, so that physicians and, where appropriate, the patient are able to use the device correctly.

Compliance shall be checked by inspection.

28.11 The accompanying documentation shall include information on avoidable HAZARDS at implantation.

Compliance shall be checked by inspection.

28.12 The accompanying documentation shall contain warning notices regarding the medical use of the device, including information about the HAZARDS caused by interference between the implantable device and other equipment likely to be used in the course of other clinical procedures or medical treatments, such as the treatments referred to in 20.2, 21.1, 22.1 and 27.1.

Compliance shall be checked by inspection.

28.13 The accompanying documentation shall warn that, if the patient with the ACTIVE IMPLANTABLE MEDICAL DEVICE subsequently is given any medical treatment in which an electrical current is passed through their body from an external source, either that the device is first deactivated, or that care should be taken to monitor the functioning of the ACTIVE IMPLANTABLE MEDICAL DEVICE during the initial stages of treatment.

Compliance shall be checked by inspection.

# Annex A (informative)

## Relationship between the clauses of this standard and annex 1 of Directive 90/385/EEC

Directive requirements		Clauses of EN 45502-1 and aspects covered	
1	The devices must be designed and manufactured in such a way that, when implanted under the conditions and for the purposes laid down, their use does not compromise the clinical condition or the safety of patients. They must not present any risk to the persons implanting them or, where applicable, to other persons.	8.1	Requires warnings to be prominent
		10.4	Requires accompanying documentation to be physically associated with the device
		19.3	Defines methodology to ensure single fault conditions are not a hazard
2	The devices must achieve the performances intended by the manufacturer, viz. be designed and manufactured in such a way that they are suitable for one or more of the functions referred to in the definition of active implantable medical device as specified by him.	10.4	Requires accompanying documentation to be physically associated with the device
		19.3	Defines methodology to ensure single fault conditions are not a hazard
3	The characteristics and performances referred to in 1 and 2 must not be adversely affected to such a degree that the clinical condition and safety of the patients or, as appropriate, of other persons are compromised during the lifetime of the device anticipated by the manufacturer, where the device is subjected to stresses which may occur during normal conditions of use.	19.2	Requires power source depletion indicator
		19.3	Defines methodology to ensure single fault conditions are not a hazard
		23.1	Defines drop test for non-implantable parts
		23.2	Defines vibration test for patient carried parts
		23.3	Sets test of tensile strength (leads, etc.)
		23.4	Requires strain relief (leads, etc.)
		23.5	Requires fatigue resistance (leads, etc.)
		23.6	Requires connections to be reliable
		26.1	Requires protection from heat from powered non-implantable parts
		28.23	Requires warning against patient entry into hazardous environments
4	The devices must be designed, manufactured and packed in such a way that their characteristics and performances are not adversely affected in the storage and transport conditions laid down by the manufacturer (temperature, humidity, etc.).	7.2	Requires sterile pack to be protected by sales packaging
		9.1	Requires markings to warn if radioactive substances are incorporated
		10.1	Requires packaging to be durable
		10.2	Requires packaging to be protected against the effects of humidity
		19.3	Defines methodology to ensure single fault conditions are not a hazard
		26.2	Requires device to be protected against the effects of temperature changes
5	Any side effects or undesirable conditions must constitute acceptable risks when weighed against the performances intended.	19.3	Defines methodology to ensure single fault conditions are not a hazard
		19.4	Requires investigation of unintended effects caused by the device
6	The solutions adopted by the manufacturer for the design and construction of the devices must comply with safety principles taking account of the generally acknowledged state of the art.	14.3	Requires investigation of biocompatibility

Directive requirements	Clauses of EN 45502-1 and aspects covered
8.iv Risks connected with medical treatment, in particular those resulting from the use of defibrillators or high-frequency surgical equipment,	20.1 Requires defibrillation protection of external ecg leads 20.2 Defines test to prove defibrillation protection of implanted device 21.1 Requires protection against diathermy, etc 22.1 Requires protection against diagnostic ultrasound 28.12 Requirement for warning notices 28.13 Requires warning about monitoring device in case of diathermy etc. 28.14 Requires warning not to expose device to therapeutic levels of ultrasound 28.15 Requires warning about the effect of therapeutic irradiation on implanted devices
8.v Risks connected with ionizing radiation, from radioactive substances included in the device, in compliance with the protection requirements laid down in Directive 80/836/Euratom, as amended by Directives 84/467/Euratom and 84/466/Euratom,	9.1 Requires markings warning of any radioactive substances 18.1 Requirement for sealed sources 18.2 Requires justification of radiation dose on patient 18.3 Requires radiation dose as low as is possible 28.2 Requires information to be provided about radioactive substances
8.vi Risks which may arise where maintenance and calibration are impossible, including excessive increase of leakage currents, ageing of the materials used, excess heat generated by the device, decreased accuracy of any measuring or control mechanism.	17.1 Requires investigation of local heating caused by faulty implanted device 19.1 Requires a design analysis 19.2 Requires power source depletion indicator
9 The devices must be designed and manufactured in such a way as to guarantee the characteristics and performances referred to in 'General requirements', with particular attention being paid to:	
9.i The choice of materials used, particularly as regards toxicity aspects,	14.2 Defines test for particulate contamination 14.3 Requires investigation of biocompatibility
9.ii Mutual compatibility between the materials used and biological tissues, cells and body fluids, account being taken of the anticipated use of the device,	14.3 Requires investigation of biocompatibility
9.iii Compatibility of the devices with the substances they are intended to administer,	(Only for infusion pumps)
9.iv The quality of the connections, particularly in respect of safety,	9.9 Requires implantable connectors to be identified on sales pack 11.8 Requires implantable connectors to be identified on sterile pack 23.6 Requires connector retention force to be specified
9.v The reliability of the source of energy,	19.2 Requires power source depletion indicator
9.vi If appropriate, that they are leak proof,	25.1 Requires implanted parts to be proof against pressure changes

Directive requirements		Clauses of EN 45502-1 and aspects covered	
14.1.viii	The month and year of manufacture,	11.4	Requires marking and defines format
14.1.ix	An indication of the time limit for implanting a device safely,	11.5	Requires marking of a 'use-before date'
14.2	Every device must bear on the sale packaging, legibly and indelibly, the following particulars, where appropriate in the form of generally recognized symbols:	10.3	Requirement that any markings shall be indelible
14.2.i	The name and address of the manufacturer,	9.2	Requires name and address of manufacturer on the sales pack
14.2.ii	A description of the device,	9.3	Requires identification of device on the sales pack
14.2.iii	The purpose of the device,	9.10	Requires supplementary description, if 9.3 and 9.4 are inadequate to declare purpose
14.2.iv	The relevant characteristics for its use,	9.4	Requires marking with characteristics sufficient to identify device
14.2.v	If the device is intended for clinical investigations, the words: 'exclusively for clinical investigations',		(Only regulatory requirement)
14.2.vi	If the device is custom made the words: 'custom-made device',		(Only regulatory requirement)
14.2.vii	A declaration that the implantable device is in a sterile condition,	9.5	Requires statement that the package has been sterilized
14.2.viii	The month and year of manufacture,	9.6	Requires marking and defines format
14.2.ix	An indication of the time limit for implanting a device safely,	9.7	Requires marking of a 'use-before date'
14.2.x	The conditions for transporting and storing the device.	9.11	Requires marking with information on any exceptional environmental or handling constraints
15	When placed on the market, each device must be accompanied by instructions for use giving the following particulars:	10.4	Requires accompanying documentation to be physically associated with the device
15.i	The year of authorisation to affix the CE mark.		(Only regulatory requirement)
15.ii	The details referred to in 14.1 and 14.2, with the exception of those referred to in the eighth and ninth, indents,	28.1 28.3 28.16 28.21	Requires name and address of manufacturer Requires description of the device Requires statement that implantable parts of a device have been sterilized Requires marking with information on any exceptional handling constraints
15.iii	The performances referred to in 2 and any undesirable side effects,	28.8	Requires information to be provided about the intended use and characteristics, and about possible side effects
15.iv	Information allowing the physician to select a suitable device and the corresponding software and accessories,	28.9	Requires information to allow selection of device, accessories and related devices
15.v	Information constituting the instruction for use allowing the physician and, where appropriate, the patient to use the device, its accessories and software correctly, as well as information on the nature, scope and times for operating controls and trials and, where appropriate, maintenance measures,	28.5 28.10	Requires provision of information on accessories that might be required to facilitate the intended use of the device Requires definitive instructions for use to be provided

# Annex B (informative)

Relationship between the clauses of this standard and the essential requirements (90/385/EEC) listed in annex A

Subclause	Relevant essential requirement	Subclause	Relevant essential requirement
7.1	7	18.1	8, v
7.2	4 and 7	18.2	8, v
8.1	1	18.3	8, v
8.2	11	19.1	8, vi
9.1	4 and 8, v	19.2	3, 8, vi and 9, v
9.2	14.2, i	19.3	1, 2, 3, 4, 5 and 9, vii
9.3	14.2, ii	19.4	5
9.4	14.2, iv	20.1	8, iv
9.5	14.2, vii	20.2	8, iv
9.6	14.2, viii	21.1	8, iv
9.7	14.2, ix	22.1	8, iv
9.8	7	23.1	3 and 8, iii
9.9	9, iv	23.2	3 and 8, iii
9.10	14.2, iii	23.3	3
9.11	14.2, x	23.4	3
10.1	4	23.5	3
10.2	4 and 7	23.6	3 and 9, iv
10.3	14.2	24.1	8, iii
10.4	1, 2 and 15	25.1	8, iii and 9, vi
11.1	14.1, iii	26.1	3 and 8, ii
11.2	14.1, i and 14.1, vii	26.2	4 and 8, iii
11.3	14.1, ii	27.1	8, iii
11.4	14.1, viii	28.1	15, ii
11.5	14.1, ix	28.2	8, v
11.6	14.1, iv	28.3	15, ii
11.7	7 and 14.1, iv	28.4	3 and 9, iv
11.8	9, iv	28.5	15, v
11.9	7	28.6	12
12.1	7	28.7	15a, iv
12.2	7	28.8	15, iii
12.3	14.1	28.9	15, iv
13.1	11	28.10	15, v
13.2	11	28.11	15, vi
13.3	12	28.12	8, iv and 15, vii
13.4	13	28.13	8, iv
14.1	7	28.14	8, iv
14.2	9, i	28.15	8, iv
14.3	6, 9, i and 9, ii	28.16	15, ii
14.4	10	28.17	15, viii
15.1	8, i	28.18	15, ix
15.2	8, i	28.19	15a, i
16.1	8, ii	28.20	15a, ii
16.2	8, ii	28.21	15, ii
16.3	8, ii	28.22	15a, iii
17.1	8, ii and 8, vi	28.23	3

- [10.3] The wet wipe test defines the requirement that the markings on the package are permanent and indelible. The requirement is based on the compliance requirement of 6.1 of EN 60601-1 : 1990.
- [10.4] The Directive requires the device to be suitable for the function stated by the manufacturer and declared to the user in the markings and accompanying documentation. This requirement would be subverted if the information could not always be correctly associated with the particular device.
- [11] In general, markings on the sterile pack should be restricted to avoid non-essential information reducing the clarity of the essential data required by this standard.
- [11.4] EN 50061 for implantable cardiac pacemakers, which has been widely accepted, has already established the requirement for the date format.
- [11.7] It is necessary for users to be able to check that they have everything they require just before implantation without first having to open the sterile pack. If the pack is left open for an undue period before implantation, the device may be subject to contamination or damage.
- [11.8] This allows final confirmation of connector types before opening the pack. (For example, the sterile pack may have become separated from the accompanying documentation.) If the pack is left open for an undue period before implantation, the device may be subject to contamination or damage.
- [12.1] prEN 868-1, the generic standard for packaging sterile products, was in preparation at the same time as this standard and has lately been issued for second CEN Enquiry.
- [13.1] This marking provides identification of the device on implant. Some implantable parts may be too small to carry all this information. Some accessories (for example, associated tools) may not need batch or serial numbering. The requirement is based on the compliance requirement of 6.1 of EN 60601-1 : 1990.
- [13.2] This requirement enables the user to group units when analysing longevity experience. Characteristics of batteries that, initially, are nominally equivalent have frequently proved to be significantly different towards the end of the lifetime of the implant.
- [13.3] This clause addresses the underlying concern expressed by the Directive for any device in use to be identified without performing a surgical operation and without requiring special equipment specific to a manufacturer or model of a device. In practice it may not be possible to suitably mark small passive devices. The present state of the art is to identify the manufacturer and model with radio-opaque symbols if the device contains a power source. Telemetry may allow identification of the serial number or date of manufacture of a device: reading the radio-opaque symbols should allow a suitable telemetry device to be selected.
- [13.4] If each device is to be used safely, giving appropriate credit to the training and knowledge of the potential user, then it has to be accompanied by key information. As far as practicable and appropriate, the information needed to use the device safely should be set out on the device itself. Where appropriate, this information should take the form of symbols, but any symbols and identification colours should conform to harmonized standards. If no standards exist, the symbols and colours should be described in the documentation supplied with the device.
- [14.1] The Directive requires implantable parts of active implantable medical devices to be supplied sterile in a non-reusable pack. If for convenience other parts are included in the non-reusable pack, they too have to be sterile to avoid contamination of the implantable parts. Material that is contained within a hermetically-sealed container throughout the lifetime of the device is not required to be sterile.
- [14.2] As well as the specified requirement that an implant does not introduce infective agents into the body, there should be no unnecessary introduction of loose particulate matter ('sterile dirt'). The method is specified so that meaningful quantitative limits can be set for assessing the results of the test. Any measuring equipment using the technique will be suitable. The test is based on a standard test for particulates given in the British Pharmacopoeia.

[19.4] Some traditional pharmaceutical clinical investigation criteria may not be applicable to active implantable medical devices: for example, age distributions and double blind controls. The scope of any clinical investigation will be restricted by the small available target population and the relatively low incidence of the target pathology.

[20.2] The circuit details in figure 1 are specified so that the energy delivered to the device, when it is directly connected to the test equipment through the 300  $\Omega$  resistor, is similar to the energy delivered to the device through the pacing lead when the subject is defibrillated using external defibrillation paddles. The specified test avoids the use of the high voltages delivered directly by defibrillator paddles. The requirement is based on clause 6 and figures 1 and 2 of EN 50061.

Defibrillation attempts often have to be repeated and the polarity of the signal introduced cannot be restricted. The subclause is intended to set a practical level of protection so that, in most cases, defibrillation will not damage an active implantable medical device. In general, it is not possible to provide absolute immunity for active implants containing semiconductors. Damage that is not apparent may cause reduced lifetime of semiconductor components. Hence the requirement for warnings in 28.13.

[21.1] This clause is intended to ensure a reasonable degree of protection from identifiable hazards such as surgical treatment or a course of physiotherapy using diathermy. (The requirement is supplemented by the lower level immunity analysis given in 27.1.) In general, it is not possible to provide absolute immunity for active implants containing semiconductors. Damage that is not apparent may cause reduced lifetime of semiconductor components. Hence the requirement for warnings in 28.13.

[22.1] Note this requirement addresses only exposure to diagnostic ultrasound. In this Part of EN 45502, exposure of an active implantable medical device to therapeutic levels of ultrasound is covered by a requirement for a warning notice (see 28.14).

[23.1] This requirement is known to be more severe than the similar requirement in EN 60601-1. Hand-held programmers and portable device analysers may be subject to severe mechanical shocks during handling by other than the expert user. If such impacts cause damage not immediately apparent to the user, the damaged device may miss-set the implant or give an erroneous analysis of an implanted device, which could subsequently result in an unnecessary explantation.

[23.2] This subclause sets a minimum standard of robustness for an active implantable medical device. The guidance provided by EN 60068 suggests that this random vibration test is more appropriate than the sinusoidal vibration test described in another Part of that standard and which was previously specified for the assessment of implanted cardiac pulse generators.

The frequency range is defined from a consideration of device usage. The low frequency limit extends to 5 Hz because implanted devices may be subjected to low frequency vibration which might excite relative movement of internal subassemblies. The high frequency limit is restricted to 150 Hz because the patient's body will tend to protect the device from high frequency vibrations which would otherwise be significant to small electronic devices.

Protection of the device during delivery and storage is provided by appropriate design of packaging.

[23.3] Implanted leads and catheters are known sometimes to be subject to tensile forces after implantation. These forces are possibly caused by bodily movements, during sporting activity, or by physical force directly applied to the body, for example during an accident.

[23.4 and 23.5] These requirements are intended to ensure adequate studies are carried out to ensure the prevention of fatigue failures of implanted leads and catheters.

[23.6] EN 45502 leaves the method of providing a secure connection to the manufacturer's specification. Thus the manufacturer is required to specify compatible connector parts (see 9.9 and 28.9) so that specified parts can be selected for test so ensuring that implanted connector pairs are reliable when subject to tensile force.

## Annex D (informative)

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| EN 552 : 1994        | <i>Sterilization of medical devices — Validation and routine control of sterilization by irradiation</i>                                   | 65/65/EEC          | Council Directive of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products.   |
| EN 554 : 1994        | <i>Sterilization of medical devices — Validation and routine control of sterilization by moist heat</i>                                    |                    | Council Directive of 20 May 1975 on the approximation of the laws of member states relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products. |
| EN 1041*             | <i>Terminology, symbols and information provided with medical devices — Information supplied by the manufacturer with medical devices.</i> | 75/318/EEC         | Council Directive of 3 May 1989 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products.       |
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\* In preparation.

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Implantable Spinal Cord Stimulators  
American National Standard  
ANSI/AAMI NS14—1995  
(Revision of ANSI/AAMI NS14—1984)

Implantable spinal cord stimulators

Developed by

Association for the Advancement of Medical Instrumentation

Approved 2 February 1995 by

American National Standards Institute, Inc.

Abstract:

This standard establishes minimum labeling, safety, and performance requirements for implantable spinal cord stimulators. Also covered are referee test methods and the rationale for the provisions of the standard.

Association for the Advancement of Medical Instrumentation

AAMI Neurosurgery Committee

AAMI Implantable Neurostimulator Subcommittee

This standard was developed by the AAMI Implantable Neurostimulator Subcommittee of the Neurosurgery Committee. Committee approval of the standard does not necessarily imply that all committee members voted for its approval. The Implantable Neurostimulator Subcommittee has the following members:

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NOTE—Participation by federal agency representatives in the development of this standard does not constitute endorsement by the federal government or any of its agencies.

## Foreword

This standard was developed by the AAMI Implantable Neurostimulator Subcommittee of the Neurosurgery Committee.

The scope of this revision has been clarified. The standard establishes minimum safety and performance requirements for internally and/or externally powered implantable neurostimulators. It covers all elements of the spinal cord stimulator system, which consists of an implanted pulse generator, connecting electrodes, and an external transmitter or programmer for transmitting energy and/or information across the patient's skin to the implanted pulse generator.

Labeling requirements have been revised and stimulation parameters have been updated in this latest edition. A standard means of testing and reporting the performance of the stimulus generator is important so that physicians are able to make informed comparisons of and selections from commercially available equipment.

The concepts incorporated in this standard should be considered flexible and dynamic. To remain relevant, this standard, like any other, must be reviewed and updated periodically to assimilate new data and to reflect advances in the technology.

This standard reflects the conscientious efforts of concerned physicians, engineers, and other health care professionals, in cooperation with manufacturers, to develop a standard for those characteristics of vascular prostheses that could be addressed at this time, in view of new technology and information.

As used within the context of this document, "shall" indicates requirements strictly to be followed in order to conform to the standard; "should" indicates that among several possibilities one is recommended as particularly suitable, without mentioning or excluding others, or that a certain course of action is preferred but not necessarily required, or that (in the negative form) a certain possibility or course of action should be avoided but is not prohibited; "may" is used to indicate a course of action is permissible within the limits of the standard; and "can" is used as a statement of possibility and capability. "Must" is used only to describe "unavoidable" situations, including those mandated by government regulation.

Suggestions for improving this standard are invited. These should be sent to AAMI, 3330 Washington Boulevard, Suite 400, Arlington, VA 22201-4598.

NOTE—This foreword is not a part of the American National Standard, Implantable spinal cord stimulators (ANSI/AAMI NS14—1995).

## Implantable spinal cord stimulators

### 1 Scope

#### 1.1 General

This standard establishes safety and performance requirements for internally and/or externally powered implantable spinal cord stimulators.

#### 1.2 Inclusions

This standard covers all electrode configurations and all elements of the spinal cord stimulation system. The system consists of an implanted pulse generator, connected electrodes placed over the spinal cord, and an external transmitter or programmer for transmitting energy and/or information across the patient's skin to the implanted pulse generator.

This standard covers electrodes implanted by a surgical procedure (a laminectomy) or introduced percutaneously. The devices (electrodes, pulse generator, and transmitter) used in the trial period of spinal cord stimulation are also included within the scope of this standard. Also covered by this standard are spinal cord stimulators that produce current affecting other areas of the spinal cord, including those stimulators that pass current through the spinal cord in an anterior-posterior direction.

#### 1.3 Exclusions

Excluded from the scope of this standard are transcutaneous electrical nerve stimulators, implantable peripheral and cranial nerve stimulators, deep brain stimulators, and external stimulating electronics directly (percutaneously) attached to electrodes placed over the spinal cord.

## 2 Normative reference

The following standard contains provisions, which, through reference in this text, constitute provisions of this standard. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this standard are encouraged to investigate the possibility of applying the most recent edition of the standard listed below.

- 2.1 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. Safe current limits for electromedical apparatus. ANSI/AAMI ES1. Arlington (Va.): AAMI, 1993. American National Standard.

### 3 Requirements

### **3.1 Labeling requirements**

In addition to the requirements of applicable federal regulations, labeling on or accompanying spinal cord stimulators shall include the following.

#### **3.1.1 Device markings**

The device shall be labeled as an implantable spinal cord stimulator. The transmitter and pulse generator shall display:

- the manufacturer's name;
- the model number;
- the serial number and/or manufacturing lot number.

#### **3.1.2 Information manual/package insert**

A physician information manual or package insert and a patient information manual (which may be combined with the physician manual) shall be supplied with each device and shall contain at least the following:

- a) prescription legend as required by federal regulations;
- b) instructions for properly unpacking the unit so as to prevent physical damage and to retain the integrity of the sterile packaging (if applicable);
- c) instructions for using the implantable spinal cord stimulator so that physicians are able to implant, test, and demonstrate the use of the device correctly;
- d) instructions for proper sterilization (or resterilization) of the implantable components. If the device is supplied sterile by the manufacturer, the method of sterilization, date of sterilization, lot number, date by which the device must be used, and proper steps to ensure that sterility is not compromised should be specified;
- e) labeling that shall include warnings, cautions, and precautions related to the use of the device, including possible interactions with other devices;
- f) a table of stimulation parameter ranges that includes at least amplitude, frequency, pulse width, and a representation of the stimulation waveform;
- g) instructions for the disposal of the transmitter and implantable pulse generator;
- h) for a device with implanted life-limiting components, a statement as to shelf life and the projected useful life of the system over a typical range of load and stimulation parameters;
- i) instructions on pre-implant testing for proper functioning.

#### **3.1.3 Registration**

The manufacturer shall provide means by which each implanted device can be registered with the manufacturer. A card to be returned to the manufacturer shall be provided with each device. This card shall provide space for:

- name;
- model number;
- serial number and/or manufacturing lot number of the device;
- patient, hospital, and physician names and addresses;
- date of implantation.

## **3.2 Performance requirements**

### **3.2.1 Electrical safety**

In accordance with 2.1, the risk current from the insulated wires shall not exceed 10 microamperes (mA) (source risk current limit, dc to 1 kiloHertz [kHz]). However, leakage currents above 100 nanoamperes (nA) may cause electrode corrosion and should be evaluated.

### **3.2.2 Stimulation parameters**

A safe and effective current to stimulate the spinal cord depends on a number of factors, including frequency of stimulation, duty cycle of stimulation, length of time of continuous stimulation, current density in the nerve, and charge per stimulation phase. The output of the device shall operate within the following parameter ranges:

- a) Pulse frequency — 1 to 1,500 pulses per second (pps);
- b) Pulse width — 1 to 1,000 microseconds (msec);
- c) Amplitude voltage (Current) — 0 to 15 volts (V) or 0 to 30 mA through a 500-ohm load.

### **3.2.3 Waveform**

The waveform shall consist of balanced positive and negative phases, so that the net dc current through the electrodes does not exceed 10 mA. (See 4.2.3.)

### **3.2.4 Controls**

Each device shall have an output-limiting control that can be set by the physician as clinical findings indicate to limit the output of the device.

### **3.2.5 Test stimulation**

If a trial period of epidural stimulation is conducted, the stimulating equipment provided for the test and the implanted device shall be capable of producing the same parameters.

### **3.2.6 Materials**

The encapsulant and/or coating of the implanted pulse generator, the electrical insulation of the lead wires, the electrode pad, and the electrode shall be composed of materials shown to be biocompatible. (See A.3.2.6)

## **4 Tests**

This section provides referee test methods that can be used to verify compliance of the device with the labeling and performance requirements of section 3. The paragraph numbers correspond, with the exception of the first digit, to those of section 3.

### **4.1 Compliance with the labeling requirements**

#### **4.1.1 Device markings**

Compliance with the requirements of 3.1.1 can be determined by visual inspection.

#### **4.1.2 Information manual/package insert**

Compliance with the requirements of 3.1.2 can be established by visual inspection, except for the electrical performance specifications required in 3.1.2(f). The test circuit of figure 1(a) or 1(b) (see next page) shall be used to measure the output characteristics.

#### **4.1.3 Registration**

Compliance with the requirements of 3.1.3 can be determined by visual inspection.

### **4.2 Compliance with the performance requirements**

#### **4.2.1 Electrical safety**

Test methods for establishing compliance with 2.1 are provided in that standard.

#### **4.2.2 Stimulation parameters**

The test circuit for all parameter measurements shall consist of a simple 500-ohm resistive load, as shown in figures 1(a) and 1(b). For radiofrequency coupled systems, the pulse generator output shall be tested at half-centimeter spacing between the transmitter antenna and pulse generator.

- a) Pulse frequency or Pulse repetition rate (PRR) is measured as the reciprocal of the interval between two consecutive pulse onsets (PI), regardless of polarity. See figure 2(a) (page 4).
- b) Pulse width (PW) is measured at the midpoint of the pulse at the maximum pulse amplitude. See figure 2(b) (page 4).
- c) Pulse amplitude (PA) is measured, at a pulse width of 200 microseconds (msec) or the nearest setting, as the linear estimate of the average value of the pulse height from the start of the pulse onset. See figure 2©.

## **Figure 1(a)—Test circuit for verifying performance specifications of externally powered stimulator**

Figure 1(b)—Test circuit for verifying performance specifications of internally powered stimulator

### **4.2.3 Waveform**

The waveform shall be observed by means of the test circuit shown in figures 1(a) and 1(b). The pulse generator output should block the dc component of current into the load. If one checks the dc = 0 volts (V) level on the oscilloscope at a high enough sensitivity, one will see the current distribution around 0 volts (see figure 3). The current averaged over the stimulation cycle shall be less than 10 microamperes (mA).

### **4.2.4 Controls**

Compliance with the requirement of 3.2.4 can be determined by inspection.

### **4.2.5 Test stimulation**

No test method required.

### **4.2.6 Materials**

Test methods are under study. (See A.3.2.6.)

Figure 2—Measurement of pulse repetition rate (a), pulse width (b), and pulse amplitude ©

Figure 3—Current distribution around 0 volts dc

Annex A

(informative)

Rationale for the development and provisions of this standard

#### **A.1 Introduction**

This standard was developed by the Implantable Neurostimulator Subcommittee of the AAMI Neurosurgery Committee. It sets forth the labeling, reporting, and performance materials requirements that the committee considered would provide reasonable assurance of the safe and effective use of implantable spinal cord stimulators for the relief of chronic pain. Like all standards, this standard reflects current technology, and as advances in the field occur, it must be modified to accommodate new data.

#### **A.1.1 Spinal cord stimulator systems**

Implanted spinal cord stimulators for pain relief are devices that electrically stimulate the nervous system, specifically, the nerve fiber tracts and/or neurons of the spinal cord. Spinal cord stimulators are used in patients to relieve severe, intractable pain of the extremities and the trunk (FDA, 1979).

Radiofrequency coupled neural stimulators, as used for spinal cord stimulation, are partially implantable pulse generator systems consisting of an external battery-powered transmitter/antenna system and a subcutaneously implanted receiver/lead system. Pulse-modulated radiofrequency energy produced by the external transmitter is radiated by the antenna. When the antenna is affixed to the skin overlying the implanted receiver, the stimulating pulses are transmitted across the skin to the implanted receiver. The receiver detects the pulsed energy and produces electrical pulses of variable frequency (repetition rate), height (amplitude), and width (duration). These electrical pulses are transmitted—via implanted, insulated lead wires with bare electrode surfaces—to the neural tissues of the spinal cord.

The stimulation pulse repetition rate, pulse amplitude, and pulse width are adjustable by means of controls on the external transmitter. For optimal efficiency, the transmitting coil of the antenna must be placed directly over and in proximity to the implanted receiver (Kahn & Maveus, 1972; Ray and Mayer, 1975). The characteristics of the stimulus pulse (e.g., amplitude) may vary with changes in antenna/receiver coupling.

"Totally implanted" pulse generators, used for spinal cord stimulation, are powered by an implanted primary (or rechargeable) battery. These devices allow stimulation to be delivered autonomously, i.e., independently of any externally worn device. Control of the implant by the patient may be accomplished by using a magnet or by using a radiotelemetry device.

Some implanted pulse generators, of both radiofrequency-coupled and "totally implanted" design, allow noninvasive selection of anodes and cathodes from an array of electrodes, hardwired to the pulse generator. These devices may be described as multichannel in common usage; technically, contemporary new devices are single-channel generators, with programmable gates to multiple outputs (North et al., 1991).

#### A.1.2 History

The idea that electrical stimulation of body organs can serve as a therapeutic modality for the modification of abnormal physiology in humans has been applied in several fields, most notably cardiology. The use of electrical stimulation of spinal cord nerve fibers in the management of chronic, intractable pain began in the 1960s.

Interest in this field was sparked by the publication of the "Gate Control Theory" (Melzack and Wall, 1965). According to this theory, sensory mechanisms for the perception of pain are controlled by a negative feedback or gating mechanism located in the spinal cord. Activated by impulse activity in large-diameter, myelinated, peripheral, cutaneous nerve fibers or their collaterals in the dorsal columns of the spinal cord, this "gate" closes to inhibit the transmission of nerve impulses from the smaller fibers associated with nociception. Although such impulse activity could be achieved by mechanical stimulation of peripheral mechanoreceptors, electrical stimulation is easier to apply. The Gate Control Theory, though later questioned, has served as the rationale for the clinical use of electrical stimulation of the nervous system as a therapeutic modality in the management of pain.

The initial clinical application of current to nerves for the relief of pain involved the stimulation of myelinated afferent nerve fibers in peripheral nerve pathways. Sheldon (1966) proposed that the pain relief observed upon stimulation of the trigeminal nerve was due to depolarization and the reduction of afferent impulses. Wall and Sweet (1967) reported that stimulation of peripheral nerves caused temporary pain relief that outlasted the period of application of current, occasionally by several hours. Sweet and Wepsic (1967) reported that peripheral nerve stimulation produced continued satisfactory pain relief in a small group of patients.

In an effort to apply stimulation to larger anatomic regions, Shealy et al. (1967) suggested that by stimulating the dorsal columns of the spinal cord, one would be able to control pain over wider areas, involving not only one extremity, but also bilateral extremities and areas of the trunk. The effect of spinal cord stimulation could be perceived over a wide area of the body in the segments below the region of the spinal cord where current was applied. The first reported use of chronic neural stimulator implants in patients took place in 1969 (Shealy et al., 1970).

Neural stimulation offers the clinician an alternative to creating destructive lesions of the nervous system, which had been the primary neurosurgical method for the management of pain.

Spinal cord stimulation may reduce the perception of pain by:

- interfering with action potential conduction, particularly at branch points of primary afferents (frequency related conduction block);
- local "gate" mechanisms in the dorsal horn, where pain signals may be blocked;
- producing effects higher in the central nervous system, possibly by the competitive "jamming" of pain signals;
- initiating an ascending-descending pain control loop that terminates in the spinal "gate";

- influencing release of endogenous factors that act on pain perception or nociception centrally or peripherally, e.g., sympathetic neurotransmitters.

### A.1.3 Electrode systems

Spinal cord stimulation initially was performed by surgically implanting electrodes via laminectomy in patients under general anesthesia. To implant the lead, part of the bony structure protecting the spinal cord was removed. The electrodes consisted of a polyester pad coated with silicone elastomer in which platinum electrodes were embedded. Electrode pads were sutured onto or below the membranes (dura or meninges) that protect the spinal cord. Depending on the location of the electrodes relative to this membrane, they were described as epi- (above), endo- (within), or sub- (below) dural (Shelden et al., 1975).

The percutaneous technique of implanting electrodes through hollow needles into the epidural space was introduced several years later. Since the patient is under local anesthesia, this procedure allows the patient to direct the clinician in the placement of leads to achieve optimal electrode location (so that paresthesias cover the entire painful area). Percutaneous trial stimulation with implanted electrodes enables the patient and the clinician to evaluate, over a period of days, the effects of spinal cord stimulation, without committing the patient to the implantation of a permanent neural stimulator (Hosobuchi et al., 1972; Erickson, 1975; Urban and Nashold, 1978).

The percutaneous implantation technique avoids the need for laminectomy, which in turn may require general anesthesia, and hence reduces the risks to the patient that accompany a major surgical procedure. With this technique, the patient's response to stimulation can be checked repeatedly during surgery, and the electrodes can be manipulated until stimulation produces paresthesias in the specific anatomic area(s) of the patient's pain.

### A.1.4 Clinical results of spinal cord stimulation

During the 1970s, numerous reports on the use of spinal cord stimulation for pain control appeared in the literature. The reported long-term results of the treatment of intractable pain with implanted spinal cord stimulators have varied widely, from a success rate of about 17% to over 80% (De la Porte, 1983; Kumar, 1991; Law, 1983; Long and Erickson, 1985; Neilson et al., 1975; North et al., 1977; Siegfried, 1982; Spiegelmann, 1991). Disinterested, third-party follow-up of a large series of patients, up to 20 years following implantation, has shown that over 50% of patients report at least 50% continued relief of pain (North et al., 1993).

Patient selection and evaluation criteria differ, and the definition of a successful outcome with stimulation is subjective. In most reports, success is defined as a reduction of the pain experience by the patient's own evaluation (Long, 1983; Young, 1978). In others, the results were considered successful if patients were able to reduce or discontinue the use of pain medications (Kravnick and Thoden, 1981; Young, 1978). Others consider work status and activities of daily living (North et al., 1993).

One pattern (common among treatments for chronic pain) appears no matter how success is defined: The effectiveness of treatment decreases with continued use (Kravnick and Thoden, 1981). Virtually all authors agree that the key to successful application of implanted stimulators is the careful selection of patients. They do not all agree, however, on which criteria are significant in predicting the success of treatment to relieve a patient's pain.

#### A.3.2.3 Waveform

Because the optimum waveform is not known, only documentation of the waveform is required. Nevertheless, the negative and positive currents must be balanced over time in order to avoid electrode deterioration.

#### A.3.2.4 Controls

See A.3.2.2.

#### A.3.2.5 Test stimulation

One reason for using temporary spinal electrodes is to test the effectiveness of the system. Therefore, the parameters for the test electrodes must be the same as those for the permanent implant. Sometimes the epidural electrodes are also the permanent electrodes, in which case the problem of equivalent parameters does not arise.

#### A.3.2.6 Materials

Criteria for biocompatibility remain a subject of scientific research. Therefore, setting specific requirements for acceptance is not a feasible or responsible approach to this issue. There have been clinical experiences with a number of materials for the receiver encapsulant or coating, the wire insulation, and the electrode pad (e.g., silicone rubber, fluorinated polymers, epoxies, polyethylurethanes, and polyester fabrics). Platinum or platinum-iridium metals have been used as materials of composition for the electrodes. New materials that have been shown to be biocompatible for use in cardiac pacemakers and cardiac pacing leads might be appropriate for use in spinal cord stimulators and thus warrant evaluation.

The assessment of the biocompatibility of materials used in medical devices depends, to a large degree, upon the end use of the device. The committee judged that an evaluation of the biocompatibility of materials for use in implanted stimulators could best be approached by reviewing the tests described in the ASTM Recommended practice for selecting generic biological test methods for materials and devices (ASTM, 1982). This standard provides a guide to the selection of biocompatibility tests based upon end use, and it discusses the significance of each test. Selection and use of any or all of these tests should be determined according to the specific intended use of the material in the implanted stimulation device; this determination is best left to the discretion of the device manufacturer. It should be noted that the tests suggested in the ASTM standard address the "effect of the material on body tissue and/or fluid."

#### Annex B

(informative)

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A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(12:31 p.m.)

CHAIRPERSON CANADY: I'd like to call the meeting back to order. This is Neurological Device Panel. We're going to be discussing this afternoon the reclassification petition for the totally implanted spinal cord stimulator.

The form the afternoon will take is we'll have a period of open comment, we'll have an FDA presentation, we'll have a presentation by the petitioner, a presentation by another industry representative, and then comments from Dr. Edmondson, from our panel, and have open discussion.

At this time, I'd like to invite any open public hearing, any public people who would like to speak regarding this issue. If none, then I'd like to introduce Dr. Kristen Bowsher, who will discuss the FDA's presentation.

DR. BOWSHER: Hi. I'm Kristen Bowsher, and I'm the lead reviewer for the reclassification petition for totally implanted spinal cord stimulators, the petitioner's advanced neuromodulation systems, or ANS.

I'd like to start by giving a brief description of the device itself. The device -- the

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1 main components are an electrode, either percutaneous  
2 or paddle, that are implanted along the spinal cord.  
3 The electrodes are connected to electrode leads, which  
4 for the totally implanted stimulators, which we're  
5 talking about today, the leads connect to a pulse  
6 generator that is actually implanted into the patient.

7 Now, the Class II devices use an external  
8 pulse generator that uses radio frequency to send  
9 signals to the receiver that is implanted into the  
10 body.

11 The intended use of the device is the  
12 treatment of chronic intractable pain of the trunk and  
13 limbs. There are currently two PMA-approved totally  
14 implanted spinal cord stimulations -- Cordis  
15 Corporation, on April 14, 1981, and Medtronic  
16 Incorporation on November 30, 1984. The petition was  
17 received from ANS by the FDA on June 16, 1999, and  
18 it's proposing reclassification from Class III to  
19 Class II.

20 Now, although we are discussing Class III  
21 totally implanted spinal cord stimulators today, I'd  
22 like to quickly review some of the regulatory history  
23 of the similar Class II radio frequency coupled  
24 devices that I've described frequently previously.

25 Back in 1978, a classification panel

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1 recommended Class II, and they identified these risks  
2 to health that they believed could be controlled by  
3 special controls. On November 28, 1978, FDA concurred  
4 in an FR Notice, and the RF coupled spinal cord  
5 stimulators have since been Class II, 510(k) devices.

6 With that as background, I'd like to now  
7 discuss the risks associated with the totally  
8 implanted spinal cord stimulators that are the topic  
9 of today's discussion. These are the MDR reports as  
10 reported in the petition from ANS. They represent  
11 only totally implanted spinal cord stimulators or the  
12 Class III devices, and were collected from the FDA web  
13 site and MAUDE and cover from 1984 to March 22, 1999,  
14 excluding 1991 because there is a problem downloading  
15 that information.

16 When looking at these, I want to stress  
17 that while these reports allow us to get a feel for  
18 the types of risks, they cannot be used to calculate  
19 rates of actual events.

20 This is a list of the risks to health that  
21 FDA has identified from information available to us,  
22 including MDR reports and literature. Note that these  
23 risks were all identified by ANS in their petition,  
24 with the exception of battery leakage.

25 The petitioner has proposed a special

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1 controls guidance document, standards, and labeling.

2 Now, I'd like to ask the panel to keep in  
3 mind the following four questions that were included  
4 in your panel packet during your discussions. Near  
5 the end of your deliberation, we will be asking you to  
6 specifically address them prior to classification  
7 recommendation.

8 The first question deals with risk  
9 identification in the patient population. The second  
10 question deals with the special controls. The third  
11 question deals with the classification itself. And  
12 the fourth question deals with the indications.

13 Thanks.

14 CHAIRPERSON CANADY: Any questions for Dr.  
15 Bowsher?

16 Then at this time, if we could have Mr.  
17 Drew Johnson, who is the Director of Regulatory  
18 Affairs for Advanced Neurological Systems. That's not  
19 true. Not really here.

20 (Laughter.)

21 DR. JOHNSON: Good afternoon.

22 CHAIRPERSON CANADY: Good afternoon.

23 DR. JOHNSON: I took my coat off because  
24 I feel a little bit more comfortable without a coat  
25 on.

1 My name is Drew Johnson. I'm Director of  
2 Regulatory Affairs for Advanced Neuromodulation  
3 Systems, Inc. And the agenda for our presentation  
4 today is as follows. I'm going to give a brief  
5 introduction to the presentation, followed by a basis  
6 for the reclassification.

7 Then, our next presenter will be Dr.  
8 Giancarlo Barolat, and he will review the device  
9 similarities and differences, as well as a summary  
10 review of the literature and risks and indications  
11 that were submitted within the petition. ..

12 And then, Dr. Tracy Cameron will give us  
13 a summary of the MDR reports, and I'll come back and  
14 go through the proposed special controls, followed by  
15 a closing statement.

16 Before I get into the risk and benefits --  
17 excuse me, before I get into the basis for  
18 reclassification, I'd like to just review some of the  
19 regulatory historical events that are associated with  
20 spinal cord stimulation. As Kristen said earlier, in  
21 1978, a panel recommended that the Class II device --  
22 that the implanted spinal cord stimulator device be  
23 classified in the Class II. In 1979, it was formally  
24 classified.

25 In 1980, a manufacturer submitted a 510(k)

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1 pre-market notification to the FDA for clearance of  
2 their internally powered spinal cord stimulation  
3 device as a Class II device, and tried to prove  
4 substantial equivalence to an external spinal cord  
5 stimulator device that was externally powered.

6 The FDA at that time deemed that the PMA  
7 -- that a PMA was necessary. This particular  
8 manufacturer at that time had the opportunity to go  
9 through the reclassification process and did not.

10 In 1981, the first implantable power  
11 generator for a spinal cord stimulator was approved  
12 through the PMA process.

13 There have been quite a few changes in law  
14 since 1984 -- 1981, and those particular changes in  
15 law really are relevant to what we're trying to do  
16 here today. There was the change -- an amendment to  
17 the Food, Drug, and Cosmetic Act in 1976, and this  
18 modification facilitated the FDA and industry having  
19 more flexibility to provide reasonable assurance of  
20 safety and effectiveness for devices.

21 In 1990, with the Safe Medical Device Act  
22 of 1990, it has instituted procedures for establishing  
23 performance standards. It required manufacturers'  
24 compliance with design controls, and, most  
25 importantly, it changed the definition of Class II

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1 devices to include the use of special controls as a  
2 means of providing reasonable assurance of safety and  
3 effectiveness.

4 And then, as recent as 1997, with the  
5 passage of the Food and Drug Administration  
6 Modernization Act, there were two key elements of this  
7 particular Act. One, post-market controls could be  
8 applied to the classification of devices to provide  
9 reasonable assurance of safety and effectiveness; and,  
10 two, the use of international standards.

11 The FDA is authorized to recognize  
12 standards and require declaration of conformance as  
13 part of the 510(k) clearance process.

14 Now, it brings us to where we are today.  
15 And through our literature review, and through our  
16 applications of special controls assigned to the risk  
17 found in our literature review, and the MDRs that we  
18 reviewed, we believe that we have a basis for  
19 reclassification of this particular device.

20 We believe that the risk and indications  
21 are similar to a Class II implanted spinal cord  
22 stimulator. We believe that general controls and  
23 special controls are available to reasonably assure  
24 the device's safety and effectiveness.

25 And last but not least, if you look at the

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1 literature -- and as shaky as MDR data is -- over the  
2 past 10 years, the use of this device certainly  
3 demonstrates that it is safe and effective for the  
4 treatment of chronic pain of the trunk and limbs.

5 Now I'd like to bring up Dr. Giancarlo  
6 Barolat to discuss the similarities and differences,  
7 as well as the literature, the risk, and indications.

8 Dr. Barolat is a neurosurgeon. He is the  
9 Director of Neurological Services at Thomas Jefferson  
10 University. He is President of the International  
11 Neuromodulation Society. He is co-editor of The  
12 Journal of Neuromodulation. He has published over 60  
13 articles in peer review journals. And it should be  
14 noted that Dr. Barolat has implanted both types of  
15 these devices for over 15 years.

16 There's one more thing I'd like to say,  
17 that our reclassification petition is not to  
18 reclassify this device outside the current  
19 classification for RF systems, which is spinal cord  
20 stimulation for the indication of the treatment of  
21 chronic pain of the trunk and limb -- trunk and/or  
22 limbs, either as a sole mitigation agent or as an  
23 adjunct to other modes of therapy used in a  
24 multidisciplinary approach. And, again, this is the  
25 same indication as the current Class II device.

1 And now I'd like to bring up Dr. Barolat.

2 DR. BAROLAT: Thank you.

3 Good morning. I'm Giancarlo Barolat. I'm  
4 Professor of Neurosurgery at Thomas Jefferson  
5 University in Philadelphia, and I have been implanting  
6 these products for about 20 years. And I have had a  
7 lot of experience with basically all of the products  
8 that have been on the market, and I have a  
9 consultantship agreement with ANS, as well as with  
10 Medtronic.

11 Now, just to give you a little overview  
12 here, what are the components of the spinal cord  
13 stimulation system? Let's start from here. The  
14 electrodes that are implanted in the spine -- without  
15 the electrodes in the spine, we would not have spinal  
16 cord stimulation.

17 Then you have the case, which is implanted  
18 in the body. Then you have the power sources, which  
19 can be inside or outside of the body. And then you  
20 have the circuitry. And as we'll see in the next  
21 slide, there are two types of circuitry. And then you  
22 have the programmers, which is what is given to the  
23 patient to control the device.

24 Now, some parts are outside of the body,  
25 and some parts are inside of the body. And as we look

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1 at the two types of systems -- the radio frequency  
2 system and the implantable pulse generator -- we see  
3 that there are some differences.

4 These are the parts that are outside of  
5 the body. In the RF system, outside of the body you  
6 have the programmer, which also activates the internal  
7 part; then you have the power source, the batteries,  
8 which are either rechargeable batteries or regular  
9 alkaline batteries; and then you have the stimulation  
10 control circuitry, which generates the signals that  
11 activate the other unit.

12 Inside of the body you have the case, and  
13 you have the decoding circuitry to receives the signal  
14 from here and sends it to the electrode. And, of  
15 course, the electrode is inside of the body.

16 In the full implantable system, outside  
17 you only have the programmer, which is what the  
18 patient is given. Inside of the body you have the  
19 case, you have the stimulation control circuitry, and  
20 then you have the power source, which is a lithium  
21 battery. And then, of course, you have the  
22 electrodes.

23 And these are the programmers that are  
24 currently under market that are given to the patient.  
25 This is the ANS programmer, which is also the patient

1 has to wear this in order to activate the system. And  
2 this is the Medtronic programmer, which is only used  
3 to change the parameters and turn the device on and  
4 off. After that, the patient does not need to wear  
5 that.

6 Besides that, the physicians are also  
7 given a different programmer, which is a more  
8 sophisticated one, which allows to change settings  
9 that are not allowed to change for the patient.

10 Now, spinal cord stimulation has been used  
11 since the late '60s. I've been involved with  
12 implanting these devices in the mid '70s. I would say  
13 that the current IPG and radio frequency systems have  
14 been in use for well over 10 years for the treatment  
15 of chronic pain.

16 And if you looked at the literature across  
17 the board, the success rate for spinal cord  
18 stimulation in the treatment of chronic pain is about  
19 50 to 60 percent. And, really, for practical  
20 purposes, when it comes down to patient's care, the  
21 main difference between the implantable systems and  
22 the radio frequency devices is the power source being  
23 on the outside for one and being on the inside for the  
24 other, and the patient having to wear the external  
25 device for the radio frequency system.

1           Now, we did a literature search to look at  
2 complications, look at the complications of spinal  
3 cord stimulation, and we found 31 articles since 1983  
4 in English that listed the complications. And we  
5 grouped the results according to the type of  
6 complications.

7           And it should be clear that from the  
8 literature it was not specified whether the systems  
9 were radio frequency or full implantable pulse  
10 generators. But some of the complications are clearly  
11 related just to the electrodes and have nothing to do  
12 with the pulse generator. Lead migration, epidural  
13 hemorrhage, with or without paralysis, leakage of  
14 cerebral spinal fluid, these have nothing to do with  
15 the pulse generator.

16           And then, infection, which in my  
17 experience is almost always at the pulse generator  
18 site, undesirable changes in the stimulation over time  
19 -- as you can see, that's a very small percentage --  
20 pain at the implant site, allergic reactions or  
21 rejection, very rare in my experience, local skin  
22 erosion over the receiver, device failure, which could  
23 be either breakage of the leads or the cables or  
24 failure of the electronic components.

25           And these are the complications that are

1 in common with both types of devices. And my  
2 experience is that the most common complications are  
3 related to the lead migration and/or infection.

4 And then complications that are exclusive  
5 to the implantable pulse generator -- from the  
6 literature search, battery failure, which, of course,  
7 you don't have with the radio frequency system because  
8 you use external batteries, and that was 1.8 percent.

9 Now, if I look in my practice -- this is  
10 what's in the literature -- if I look in my practice,  
11 I have implanted maybe 1,500 of these systems since  
12 1985, and there is two additional complications that  
13 I have had that are exclusive to the IPGs. And one is  
14 leak of the acid in the battery, which occurred in a  
15 device that actually never went to market and has not  
16 been implanted since maybe eight or nine years. And  
17 I had a few instances of that, just with that one  
18 device.

19 And then I have had occasional patients  
20 who have received jolts, power surges, when they go  
21 through metal detectors or those theft deterrent  
22 devices in the supermarkets.

23 I would say that in my experience the  
24 infection rate, the pain at the sites, is about the  
25 same for both the radio frequency and the pulse

1 generator.

2 What are the indications for spinal cord  
3 stimulation? I would say that the indications are  
4 shared between the two types of systems. Chronic pain  
5 makes up for the bulk of it, and the different  
6 subcategories of chronic pain -- RSD, causalgia --  
7 they are part of the complex regional pain syndromes.

8 And then different pains -- neuropathy,  
9 brachioplexis, nerve root avulsion, failed back  
10 surgery -- as you know, that probably makes up for  
11 more than half of the implants today in the United  
12 States -- neuralgias, arachnoiditis, and then pain due  
13 to peripheral vascular disease, and pain due to  
14 angina, which are two relatively more recent  
15 applications.

16 What are the contraindications to the  
17 procedure? Well, we usually do a trial before we do  
18 the implant. And, obviously, if the patient does not  
19 obtain pain relief, that's a contraindication to the  
20 implant. A second contraindication is if the patient  
21 cannot understand -- comprehend how you operate the  
22 device, then unless you have somebody else that can do  
23 it for him, then I would not implant somebody.

24 And then there is limitations in patients  
25 who have cardiac pacemakers, and certainly patients

1 who have to have MRIs should not have the implants.

2 What are the benefits of having the total  
3 implantable system versus the radio frequency system?  
4 Well, there are several advantages, as you can  
5 imagine. There is no external hardware that should be  
6 worn all the time. So it's more appealing  
7 cosmetically. There is no restrictions to what you  
8 can wear. You can go in the water and still have the  
9 benefit of the stimulation, where with the radio  
10 frequency system, if you go in the water, you have to  
11 remove the antenna and so you cannot have the  
12 stimulation.

13 And then you don't have to use the  
14 antenna, and that's a major factor because if you're  
15 perspiring, for instance, then the antenna will not  
16 stick to the skin. And so you cannot use it.

17 And also, you don't have to go through the  
18 trouble of making sure that the antenna is aligned  
19 with the device in the body, and he moves just a  
20 little bit then you might lose a stimulation, or it  
21 might be too strong. So there are definite advantages  
22 to having a totally implantable device.

23 So in my opinion, when I look at all of  
24 the pros and cons, I would say that, first of all,  
25 both the radio frequency devices and the totally

1 implantable devices share the same indications. And  
2 for practical purposes, when I discussed this with the  
3 patient, the main difference, at least for the  
4 patient, is the fact that the power source is on the  
5 outside instead of being on the inside.

6 Also, when I review my complications,  
7 outside of those specific ones that I mentioned that  
8 are related to the internal battery, the other  
9 complications are basically very similar for the two  
10 types of systems. And the other very important  
11 consideration is that having the inside battery --  
12 sure, it carries a little bit of a risk, but it's less  
13 than the risk of having to do repeat surgeries to  
14 replace it. That risk is well worthwhile.

15 And that's the end of my presentation.

16 MS. CAMERON: Hi. My name is Tracy  
17 Cameron. I am a Senior Scientist with ANS, and I'm  
18 going to report on the MDR search that we did.

19 Before I start talking about the specifics  
20 to our search, I'm going to talk a little bit about  
21 MDRs. First of all, MDRs are incident reports, and  
22 these alleged incidents are placed into categories at  
23 the time of entry, before any analysis has been done.

24 The categories that are used are death,  
25 serious injury, and malfunction, and usually these are

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1 placed into these categories by the manufacturer  
2 themselves.

3 In order to do -- because these events are  
4 alleged incidents, in order to do a proper analysis of  
5 the database you are required to actually review each  
6 individual report and assess what actually happened in  
7 those cases. If you don't do that, it can lead to a  
8 high level of false positives when you're looking at  
9 these MDRs.

10 And I have an example of one that -- I  
11 hope you can see it, but I think you have -- you might --  
12 have it in your handouts. This is an example of an  
13 MDR that was pulled up looking at spinal cord  
14 stimulation. Now, this MDR could be placed in the  
15 category of an IPG. However, upon further  
16 investigation, we found that this is actually an RF  
17 system. So it would be misrepresenting to put it in  
18 with IPGs.

19 Also, if you look, it's been reported as  
20 a death, which means -- which would imply that the  
21 device had something to do with the death of the  
22 patient. However, when you read the description, you  
23 see that it says there was -- that they did not feel  
24 that there was enough information to suggest that the  
25 product actually contributed to the death of this

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1 patient.

2 So using this MDR without reviewing it in  
3 detail may cause people to think that an IPG would  
4 have caused the death in this situation. And  
5 actually, like I said, this isn't even an IPG.

6 Now, I'm just going to go over how we did  
7 our MDR search. We used MDR and MAUDE searches, and  
8 we performed a search using manufacturers' names and  
9 the term "neuro." This gave us a total of 1,386  
10 reports from the time 1984 to 1999. We started with  
11 1984 because this is when the most -- the currently--  
12 available IPG system came on the market.

13 This search was further refined by  
14 identifying those reports which only talked about IPG  
15 systems. So we excluded all RF systems from our  
16 search. And also, we only included those IPG systems  
17 which are currently in commercial distribution because  
18 they have had the longest duration, the longest time  
19 out in the market.

20 We found a total of 408 reports when we  
21 did this, and we categorized them according to adverse  
22 events, and we used the same risks that were found in  
23 the literature review. This allowed us to compare the  
24 two types of searches.

25 However, there was a problem when looking

1 at the MDRs, and that is that often there is not  
2 enough information in the MDRs to place it in a  
3 category. They just don't have enough information in  
4 them to determine what you -- put it where you want to  
5 put it or where it should go.

6 And I'm going to show you an example of  
7 one that we found, and what we did with them was we  
8 placed them in an "other" category because we just  
9 couldn't say anything. And this one, it says that the  
10 device -- that it was explanted because of a possible  
11 failure. So we couldn't determine where that should  
12 go.

13 Now, the results of our search were we had  
14 the largest category in "other" -- 144. The second  
15 largest was related to undesirable changes in  
16 stimulation over time. The third was related to  
17 battery failure. However, they were all pre-end of  
18 life battery failure in our search. The fourth  
19 category was device failure, and this included -- we  
20 included lead breakages, hardware malfunctions, and  
21 loose connection in this category.

22 Fourteen reports were related to  
23 infection, 10 to pain, two to skin erosion, and we had  
24 one lead migration, one seroma, and one allergic  
25 reaction.

1 Basically, from our MDR search, we did not  
2 find any new risks that hadn't already been identified  
3 in the literature search.

4 Before I finish, I just want to say that  
5 there were limitations to our MDR reporting. And the  
6 first one is that we obviously couldn't include events  
7 that went unreported. Also, the other limitation was  
8 that there were a number of incomplete reports, which  
9 we had to group in the "other" category. There was  
10 not enough information.

11 Third, we don't know what the total number  
12 of devices that were implanted over these years were,  
13 so we have no denominator for the numbers.

14 And, finally, as was mentioned earlier,  
15 the MDRs for 1991 were unavailable due to a problem  
16 with the MDR database.

17 Now I'm going to introduce Drew again.  
18 He's going to talk about special controls.

19 DR. JOHNSON: Again, Drew Johnson,  
20 Director of Regulatory Affairs for ANS. How are we  
21 doing on time, Madam Chair?

22 CHAIRPERSON CANADY: You've got about  
23 seven or eight minutes.

24 DR. JOHNSON: Okay. I'll try to run  
25 through this.

1 Just to refresh everyone's memory about  
2 Class II devices and how are they defined, because  
3 it's paramount to what we're trying to do here today.  
4 And as I said earlier, the Safe Medical Device Act of  
5 1990 really changed the definition of the Class II  
6 device to be what you see there, and that is a  
7 Class II -- the devices in Class II, the general  
8 controls alone are insufficient to provide reasonable  
9 assurance of the safety and effectiveness.

10 And there is sufficient information to  
11 establish special controls, including the promulgation  
12 of performance standards, post-market surveillance,  
13 patient registries, development and dissemination of  
14 guidelines, recommendations, and other appropriate  
15 actions as the Commissioner deems necessary to provide  
16 such assurance.

17 ANS has identified several risks from the  
18 literature. And using the information as we best  
19 possibly could from the MDR data, and from these  
20 risks, we have assigned special controls. I'm not  
21 going to go through each one.

22 The point here is that for the risk that  
23 we found, we were able to find a multitude -- a  
24 multitude of special controls, not one for each risk  
25 but a multitude.

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1 And Tracy and Dr. Barolat went through the  
2 risks in the literature, so I'm not going to bother  
3 you with going back through that. But these are the  
4 same risks that were listed in the petition.

5 I'd like to talk a little bit about the  
6 risk of battery failure, and how that relates to the  
7 petition and our device. Of course, there is an  
8 internal battery within the totally implanted spinal  
9 cord stimulator, and we don't want to make light of  
10 that or pretend that that's a simple issue.

11 However, since the laws have changed over  
12 the years, we believe that there are standards  
13 available that cover both implanted and explanted  
14 devices. As a matter of fact, the ANSI standard, the  
15 participants from the opposition, had an opportunity  
16 to participate within the development of that  
17 standard, and also other industry representatives and  
18 users in the field.

19 A year or so ago, there was an  
20 international standard that was harmonized. It's  
21 called the Active Implantable Medical Device Standard.  
22 It's EN 45502. That particular standard is available.  
23 And by the way, that standard is accepted for use on  
24 not only a device like a spinal cord stimulator but  
25 for other devices that are more life-threatening.

1 And you say, "Well, that's all well and  
2 good. But what about the standards that we use here  
3 in the United States and the controls for that?"

4 DR. GONZALES: Excuse me. I'm sorry.

5 DR. JOHNSON: Yes.

6 DR. GONZALES: You said the standard for  
7 implanted and explanted. Do you mean implanted and  
8 external?

9 DR. JOHNSON: External. I'm sorry.

10 DR. GONZALES: Okay.

11 DR. JOHNSON: I'm sorry. Implanted and  
12 external. I'm trying to meet Madam --

13 CHAIRPERSON CANADY: You're doing okay.

14 DR. JOHNSON: -- Chairman's time here.

15 (Laughter.)

16 CHAIRPERSON CANADY: It's not that strict.

17 DR. JOHNSON: Okay. All right.

18 CHAIRPERSON CANADY: You are the  
19 petitioner.

20 DR. JOHNSON: All right. Thank you.  
21 Thank you, Madam.

22 Other controls that are available for this  
23 type of device are specific labeling controls, which  
24 would include warnings, precautions, and adverse  
25 events within the labeling. I might add that these

1 warnings, precautions, and adverse events that we are  
2 proposing here are the same ones that are available  
3 now for the Class II device, the same ones that are  
4 available for the Class III device.

5 I'm not going to go through each one, but  
6 the FDA can make the determination as to what specific  
7 labeling should be required as that control.

8 And last, on the labeling slide here, is  
9 the standard prescription statement.

10 And here are some labeling controls that  
11 are unique to the internal battery. We believe that  
12 manufacturers shall provide a chart or calculation in  
13 the physician's manual which would illustrate the  
14 range of estimated service life of the device for  
15 various output selections.

16 We believe that manufacturers should have  
17 a low battery indicator on the patient programmer-user  
18 interface. We believe that manufacturers should have  
19 an end of battery life indicator on patient programmer  
20 interfaces.

21 Let's talk a little bit about internal  
22 battery. People who are not used to design processes  
23 may say, "Well, you're trying to put a battery on  
24 someone. How are you going to control that and make  
25 sure the manufacturers out there can adequately

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1 control that and make sure that it is safe?"

2 Well, because of some of the laws that we  
3 talked about, there are now things in place that allow  
4 manufacturers to do that. Design controls were  
5 initiated. There are standards, like risk assessment  
6 standards, the EN 1441 harmonized standard.

7 There are safety standards, like the EN  
8 45502. And then sometimes manufacturers have to go to  
9 other standards based on risk assessment and  
10 specifications, based on their risk assessment of  
11 devices. And then, again, there is labeling. —

12 Now, if a manufacturer is making a device  
13 -- say, the implanted spinal cord stimulator with a  
14 battery in it -- and he thinks that the battery is a  
15 risk because it's implanted, that manufacturer would  
16 use a risk assessment which is based on the EN  
17 standard and a recognized standard that the FDA  
18 recognizes.

19 And this is some of the ways that a  
20 manufacturer out there in our world would go about  
21 determining how they are going to identify what those  
22 issues might be, what are the risks to those issues,  
23 what kind of controls can they use to mitigate those  
24 issues. This is how it works, and this is how we can  
25 use the EN standard for risk assessment and other

1 specific standards.

2 As I said before, there is a standard that  
3 was established and reestablished, really, back in  
4 1995, and this standard established safety and  
5 performance requirements for internally and/or  
6 externally powered spinal cord stimulators. There's  
7 the recently approved and harmonized EN standard that  
8 I talked about a little bit earlier.

9 And then there's the standard that's a  
10 risk assessment standard, and I'd just like to spend  
11 a few moments talking about the bullet points that I  
12 have here and how this relates to what I discussed in  
13 the previous slide on risk assessment.

14 This particular standard specifies the  
15 procedure for the manufacturer to investigate, using  
16 available information, the safety of medical devices,  
17 including in vitro diagnostic devices and/or  
18 accessories. It's used to identify hazards, estimate  
19 the risks associated with that device. It also is  
20 used to assist in areas where relevant standards are  
21 not applicable or not used.

22 This is how a manufacturer goes through  
23 the process that I talked about earlier, identifies  
24 the risk, identifies the hazards, the risk associated  
25 with it, and then the manufacturers -- it's on the

1 onus of the manufacturer -- to go in and define what  
2 kind of special controls are controls in the  
3 manufacturing process, or standards or specifications  
4 that he can use to mitigate that risk.

5 And by the way, FDA requires, through pre-  
6 market notification, and in some PMAs, that this  
7 information is provided.

8 Other controls are guidance documents.  
9 And, again, we're not talking about one or two  
10 guidance documents that can control these particular  
11 risks. We're talking about several. . . Most-  
12 importantly, I think because of the importance of the  
13 implanted device, the high technology of the implanted  
14 device, there are guidance documents that can handle  
15 that, along with special controls such as standards.

16 Again, we're here today to ask the panel  
17 to consider reclassifying this device to a Class II.  
18 We believe that the risk and indications are similar  
19 to Class II implanted spinal cord stimulators. We  
20 believe that there are general controls, an abundant  
21 amount of special controls that are available to  
22 reasonably assure the device's safety and  
23 effectiveness.

24 We also believe that we've shown -- and if  
25 you read it yourself, you will see that over 10 years

1 of use demonstrates that this device is safe and  
2 effective for the treatment of chronic pain of the  
3 trunk and limb. And it's important here that we're  
4 not trying to get into angina, we're not trying to get  
5 into sacral nerve root stimulation. We're talking  
6 about the same indication, that this is the device  
7 that has been used for a number of years.

8 And last, I'd like to say that I believe  
9 that reclassification of this device is good for the  
10 FDA. I think long term it may spur competition, which  
11 may drive prices down, which would be good for the  
12 consumer.

13 And last, but not least, I believe that  
14 the special controls that are not in place today, not  
15 1981, not 1991, we're talking about today, that these  
16 special controls will not allow devices to be put into  
17 the market that will cause any more harm or risk to  
18 patients than the current Class II device.

19 Thank you.

20 CHAIRPERSON CANADY: Thank you very much,  
21 Mr. Johnson.

22 Any of the panelists have any questions  
23 for any of the ANS speakers? Dr. Hurst?

24 DR. HURST: Yes. Can you tell me the  
25 battery life of these implanted stimulators?

1 DR. JOHNSON: I'd like to bring up our  
2 research development -- this is John Erikson, our Vice  
3 President of Research and Development.

4 MR. ERIKSON: John Erikson, ANS. It  
5 depends on the battery capacity that's in the cell  
6 that you put in the device. So it's by design, how  
7 big a battery you have. I'm not sure --

8 DR. HURST: I mean, what are we talking  
9 about, a couple of years?

10 MR. ERIKSON: It depends on the  
11 parameters. It could be two to five years. Could be  
12 less if you turn the -- all of the parameters wide  
13 open.

14 DR. HURST: I see. And how does that  
15 compare with the ones that are currently available?

16 MR. ERIKSON: Are you talking about our  
17 device or --

18 DR. HURST: You don't have any currently  
19 available, I don't --

20 MR. ERIKSON: We don't have one currently  
21 available, correct.

22 DR. HURST: The ones that are on the  
23 market now, how does that --

24 MR. ERIKSON: It would be equivalent or --

25 DR. HURST: -- with the battery --

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1 MR. ERIKSON: -- bigger battery than  
2 what's currently on the market.

3 DR. HURST: It's a bigger battery?

4 MR. ERIKSON: Yes.

5 DR. HURST: How much bigger?

6 MR. ERIKSON: We currently have a --

7 DR. HURST: I'm just trying to get a feel  
8 for how long the battery --

9 MR. ERIKSON: About 30 percent bigger.

10 DR. HURST: Okay. So that would be, what,  
11 a one- to four-year battery is available now, and this  
12 would be a two- to five-year -- I'm not trying to hold  
13 you to the numbers. I'm just trying to get a feel for  
14 how often --

15 MR. ERIKSON: If you use equivalent  
16 settings, correct.

17 DR. HURST: I see. Okay.

18 CHAIRPERSON CANADY: Dr. Walker?

19 DR. WALKER: As long as you're up there,  
20 let me ask you another question.

21 MR. ERIKSON: Okay.

22 DR. WALKER: There is another type of  
23 implanted pulse generator that's used for the  
24 treatment of radiocardium, more commonly known as a  
25 cardiac pacemaker. From a manufacturing/engineering/

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1 quality control point of view, from what goes inside  
2 -- because they both look the same -- what's the  
3 difference between a spinal cord stimulator and a  
4 cardiac pacemaker, other than different rates,  
5 different outputs?

6 DR. ERIKSON: I have the experience, but  
7 Medtronic would probably be better to answer that.  
8 But I'll try and answer that.

9 I believe they would be the same. At  
10 least what we're designing and building will be the  
11 same identical controls in place as the cardiac  
12 pacemaker. The EN standard is used for cardiac  
13 pacemakers, and we would be -- we're using that  
14 standard for our development.

15 DR. WALKER: As a followup, are cardiac  
16 pacemakers Class II or Class III devices?

17 MR. ERIKSON: Cardiac pacemakers are  
18 Class III devices. They are a life-sustaining  
19 product.

20 CHAIRPERSON CANADY: Ms. Maher?

21 MS. MAHER: I'd just like to take this  
22 opportunity to remind the panel that we're not looking  
23 at any particular device but a classification of  
24 device. So while it might be important to look at  
25 what type of battery lives we're talking about, it's

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1 not important specifics.

2 DR. GATSONIS: One item that was brought  
3 up is the risk of additional surgeries because the RF  
4 device fails versus the risk of battery failures in an  
5 IPG. Do you have any data that quantifies this?

6 DR. JOHNSON: Could you repeat that  
7 question?

8 DR. GATSONIS: Do you have any data on --

9 DR. JOHNSON: The whole question. Excuse  
10 me. I'm sorry.

11 DR. GATSONIS: Yes. What I wanted to say --  
12 is that one of the key -- one of the items that seemed  
13 key to me in making the comparison between IPGs and  
14 RFs -- or FRs or whatever it -- is the risk of  
15 additional surgeries that will happen because, say, an  
16 RF fails versus the risk of, say, a battery failure in  
17 an IPG.

18 In other words, what is it ultimately that  
19 you gain by the IPG? And what extra risks do you  
20 generate? It seems to me that that is sort of one of  
21 the salient questions in terms of answering the issue  
22 of reclassifying this.

23 DR. JOHNSON: Okay.

24 DR. GATSONIS: Do you have any data, any  
25 numbers, about this?

1 DR. JOHNSON: I'll let Dr. Barolat answer  
2 the question, but I'd like to clarify your question.  
3 I think you meant that, what's the difference between  
4 the IPG, which has the battery and the shorter life  
5 span -- the external device, the battery is on the  
6 outside, so you just change the battery on the  
7 outside. The internal device has the batteries --

8 DR. GATSONIS: Yes, I understand.

9 DR. JOHNSON: -- on the inside, so you --

10 DR. GATSONIS: I understand. I noticed in  
11 Dr. Barolat's presentation you were mentioning the  
12 risk of extra surgeries needed for RF devices. Do you  
13 have any quantitative data on this?

14 DR. BAROLAT: Well, the risk of replacing  
15 the battery -- with internal pulse generator, it's a  
16 guarantee with the currently available systems that  
17 you will have to replace the battery. So you  
18 guarantee that every X number of years you have to  
19 have an operation.

20 With the radio frequency system, you  
21 don't. Unless the system fails, you never have to  
22 have another operation.

23 DR. GATSONIS: Okay.

24 DR. BAROLAT: The risks of replacing the  
25 battery, of the surgeries that you would do

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1 repetitively, in my experience are minimal. Really,  
2 the main risk is infection because there is no risk of  
3 damage to the nervous system because you're just  
4 operating under the skin.

5 So the main risk is infection, and I would  
6 say my experience -- the infection, by changing the  
7 batteries, is maybe two percent, let's say. So it's  
8 a very small risk.

9 DR. GATSONIS: Okay.

10 DR. BAROLAT: And you have to pitch that  
11 against the advantage of being able to use the  
12 stimulator more effectively for the patient.

13 DR. GATSONIS: Okay. Then I  
14 misunderstood, because I thought I understood you to  
15 say that the IPG has less of a risk -- I mean, saves  
16 in repeated surgeries down the line. I misunderstood  
17 you.

18 DR. BAROLAT: No, no, no, no. With the  
19 IPG, you're guaranteed --

20 DR. GATSONIS: You're guaranteed --

21 DR. BAROLAT: -- that you will have to  
22 have --

23 DR. GATSONIS: That's what I thought.

24 DR. BAROLAT: -- serial surgeries down the  
25 line.

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1 DR. GATSONIS: Yes. That's what I  
2 thought. Thank you.

3 The other question that I had was for --  
4 when you were presenting the MDR data, you limited the  
5 search to the IPGs, correct? Do you have similar data  
6 for the RFs, to see how some of these relative risks  
7 go?

8 MS. CAMERON: No, we didn't.

9 DR. GATSONIS: Because those RFs are  
10 relevant. I mean, if you were going to make a  
11 comparison between IPGs and RFs, I would have expected  
12 you would have looked at the RFs and you would have  
13 two columns of numbers there.

14 MS. CAMERON: No, we didn't do it. Not  
15 for the MDRs we didn't do that. Just for the -- we  
16 did it for the literature only.

17 CHAIRPERSON CANADY: Other questions from  
18 panelists? Thank you very much, ANS.

19 We'll now have a presentation from Mr. Bob  
20 Klepinski, the regulatory counsel for Medtronic. Go  
21 ahead, sir.

22 MR. KLEPINSKI: Good morning. I am Bob  
23 Klepinski from Medtronic. I'd like to talk in  
24 opposition to the petition today. Some of you here  
25 may think it unusual that a manufacturer would take a

1 step which would appear to be asking for more  
2 regulation rather than less. And that's not our  
3 position.

4 If there was a general attempt on the part  
5 of the FDA to simplify PMAs for these devices, and to  
6 do an easier route to market, we'd certainly work with  
7 the FDA and be all in favor of that. What we oppose  
8 is carving off this one indication from the rest of  
9 the implantable Class III neurological devices and  
10 putting in a separate class. And I'll talk a little  
11 bit more about my reasons for that.

12 Starting out, also, Medtronic feels  
13 extremely complimented by all of the things said by  
14 petitioner and by the FDA. In essence, what you've  
15 heard today is a fact that since Medtronic is good at  
16 this, and we've done it successfully for 10 years, we  
17 should simplify the system. In essence, we've had a  
18 system that worked well for 10 years, so we should  
19 junk it.

20 I think there's a lot of reasons not to do  
21 that, and that's what I'd like to talk about today is  
22 the -- the risk to patients that weren't discussed in  
23 any of the previous materials, and the risk to  
24 patients that we have to consider from active  
25 implantables.

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1 And we have to put patients first here,  
2 and we have to consider what can happen to patients.  
3 That's our Medtronic focus. And I want to look at  
4 some of the differences from a slightly different  
5 point of view than you've seen in the previous  
6 presentations.

7 Now, we're going to look at -- through  
8 this presentation -- through some of the pre-market  
9 PMA controls and their effect. We're going to look at  
10 some of the post-market PMA controls and how they have  
11 controlled patient risk, and also the MDR and adverse  
12 event reporting issues.

13 Now, the one big issue is the difference  
14 between an implantable Class 3 device, an active  
15 implantable as they are termed under the European  
16 community, and RF devices.

17 Now, we've heard today that the difference  
18 is a power source. That's sort of like saying the  
19 difference between a Conestoga wagon and a modern  
20 automobile is that there's a battery in the latter.  
21 I mean, it's true that there's a battery, but there's  
22 a lot more to it.

23 There's a lot of technology involved in  
24 this, and Medtronic, I have to say, is good at this.  
25 We've successfully done it. We worked under the PMA

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1 system. We know how to do this. And we also know how  
2 complex it is.

3 And the one major difference that I want  
4 you to think about is that when you're talking about  
5 failure modes, the RF device is essentially passive  
6 inside the body. If there is any programming issue  
7 with the external device, if there is any malfunction,  
8 you take away that external device and you're left  
9 with a passive plastic encapsulated inert thing in  
10 your body.

11 With an active implantable, the active  
12 implantable is performing things in the body under  
13 programming control. And you cannot simply take away  
14 the RF antennas and the external device. It is  
15 working away inside your body. If the reason is that  
16 it is out of control, explant is the cure.

17 Now, these have not been an issue in the  
18 10 years, the slice of data looked at here today. And  
19 the reason is is we're darn good at this. We have not  
20 had problems in those areas. But that does not mean  
21 it's an issue that does not need control through the  
22 PMA process.

23 Now, some of the things that can happen  
24 are the device can malfunction. I mean, there can be  
25 circuitry issues. And somebody asked earlier today

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1 about pacemakers, and this is very analogous. There  
2 have been pacemaker companies that had circuitry  
3 issues that caused their devices to do strange things.  
4 The same can happen with neurological devices and did  
5 happen in our predecessors.

6 Battery failure is not battery failure  
7 that is running down. I mean, it's a well-known  
8 phenomena. We know more about implantable batteries,  
9 I contend, than any other company in the world.  
10 There's one other real good manufacturer, but we know  
11 the most, we know how to characterize them. . .

12 But this is not an easy thing, and the  
13 battery leakage the FDA talked about can bring on  
14 patient effects that are very serious. And this is in  
15 a device which is operating on its own.

16 There can be programming failures. As  
17 we'll talk later, there's telemetry back and forth  
18 from a programmer to the inside, and the inability to  
19 program may leave you with a patient with a device  
20 that has to be explanted.

21 Stimulation parameters have been known to  
22 change on their own on some failed devices. And all  
23 of these can have various other patient sequelae.

24 Now, you've probably seen all you ever  
25 want to hear in the world about the difference between

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1 implantables and external. So I'd like to skip  
2 through these parts fairly quickly.

3 But I want you to understand that the big  
4 difference is that with the implantable device, it is  
5 running on its own inside that body, and the control  
6 is through telemetry. There is no antenna to take  
7 away to shut it off. The device is operating on its  
8 own.

9 Now, an implantable device is incredibly  
10 more complex also than the RF device is. There is  
11 some circuitry in an RF device, but the difference  
12 here in having an implantable battery that you have to  
13 seal -- welding may sound like a rather benign topic  
14 to most of you, but sealing batteries is a very  
15 significant item, and the failures we'll talk about  
16 later resulted from that area.

17 Having circuitry that's going to stand up  
18 inside the body and operate on its own and keep  
19 telemetry out is a very difficult art. The sealing up  
20 of the can, the hermetic sealing of the exterior metal  
21 can is something we're good at. We haven't had  
22 failures in that, but there are pacemaker companies in  
23 recent years that had to have major recalls because of  
24 failures in sealing. These are not things to be taken  
25 lightly.

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1           So, once again, an RF device receives  
2           their power from the outside. The circuit is a simple  
3           one to receive that power and send it through the  
4           body. When you take that RF antenna away, there is  
5           nothing going on inside your body.

6           In the IPG devices, the antenna is a radio  
7           communication sending not power but information in.  
8           The circuit inside is acting on its own, controlling  
9           the stimulation parameters. So you are dependent on  
10          the technology in that circuit.

11          So if there's a failure inside there, you--  
12          can't stop it by simple external action. You have to  
13          put the programmer on and reprogram it. If the  
14          failure happens in a programming area, such as had in  
15          some past devices, then you cannot fix the problem;  
16          explant is the only solution.

17          So there is a degree of risk in active  
18          implantables that is different. And, of course,  
19          there's an internal power source, with all of the  
20          attendant issues, and there's an emergency stop. You  
21          have to have a way to do it through telemetry.

22          Now, I want to go on to talk about -- a  
23          little bit about the history of this. But we have to  
24          talk history briefly and issues that didn't come up in  
25          the other presentations.

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1           You saw a history chart that had notable  
2 events, among them the success of Medtronic in doing  
3 this. You saw one other mention of one other company  
4 in there. And I'd like to talk about that company and  
5 one other attempt.

6           In essence, to my knowledge, there have  
7 been three companies that tried to do this. Two have  
8 failed dramatically with FDA interaction. All of the  
9 data you've seen today is a result of the fact that  
10 Medtronic is good at this and it's our data. You've  
11 not seen anything to do with the two failures.

12           Cordis was mentioned here. Cordis is a  
13 pacing manufacturer and an implantable neurological  
14 manufacturer, like Medtronic, who was working on this  
15 around the same time as Medtronic started this  
16 project. They had serious battery failure problems.  
17 They had leakage problems. It caused the FDA to take  
18 fairly dramatic regulatory action against them.

19           Those products were removed from the  
20 market. The company was essentially out of business.  
21 It was sold to a pacing competitor and is no longer  
22 here. That device is gone.

23           The second company that went on to define  
24 an active implantable for neurological uses also had  
25 battery problems. That company had an IDE. When FDA

1 went in for the pre-market approval inspection, part  
2 of the PMA process, there's a large 43 issue.

3 I don't know if you folks are used to  
4 seeing 43s. They are often a page, maybe two. I've  
5 seen some fairly big ones, but this --

6 CHAIRPERSON CANADY: I'm not sure  
7 everybody knows what a 43 is.

8 MR. KLEPINSKI: Oh. A 43 is the FDA  
9 observations of what they consider may be potential  
10 violations at a site, done by the field office. This  
11 43 happened to the third company that tried to make  
12 these devices.

13 After that, there's a regulatory letter.  
14 The FDA terminated the IDE. The device never came to  
15 market. So, once again, three people have tried to do  
16 this. Two have failed dramatically with FDA  
17 intervention. We have succeeded. All the data you've  
18 seen today has been about our success. So we don't  
19 believe, based upon that, that this system is ripe for  
20 a change to let anybody do this through the 510(k)  
21 process.

22 Let's talk a little bit about adverse  
23 events. Now, I'm not sure how the data was developed  
24 in this search. We went out after we saw this  
25 petition and did an MDR search. We did a search for

1 spinal cord stimulation. We found there are some 400  
2 or so mentioned in the petition. We found well over  
3 2,000.

4 When we then went and split them into IPG  
5 and RF, as we thought we were using the same format as  
6 petitioner, they had a few hundred and we found 700.  
7 So there is a story here that you're not seeing.

8 And one is, I'll say exactly as petitioner  
9 did, you can't rely on MDR data for making your  
10 decision, because there's all kinds of things that  
11 cause MDRs. I mean, there can be different physician  
12 techniques. There can be patient interactions.  
13 There's a lot of reasons to file them, so there is a  
14 base number. You can't go by it, but two things to  
15 remember.

16 One, the MDR information you're looking at  
17 was Medtronic MDR information, on a system that worked  
18 well, didn't include the drastic failures. In fact,  
19 one of the things in this 43 was that they were not  
20 filing adverse event reports. And, therefore, there  
21 are no adverse event reports for you to look at for  
22 that -- for the failed history.

23 But the thing to look at is whether, you  
24 know, when you look at the differences between what  
25 was found in the searches whether, indeed, is

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1 information before you. One of the issues you have to  
2 consider is that the statutory standard is not just  
3 the life supporting that was talked about for  
4 pacemaker devices.

5 There's two reasons to be in Class III.  
6 There's implantable or life-sustaining or supporting.  
7 If you're going to change an implantable device, the  
8 statute says you have to have sufficient information  
9 to show that special controls are going to be  
10 sufficient. And I don't think you have it in front of  
11 you because you haven't even seen the adverse history.

12 Now, one other issue to discuss today is  
13 what is being down classed? There has been much talk  
14 of this as being a device, but you're not talking here  
15 today about down classing a device. You're talking  
16 about down classing an indication.

17 Now, the IPG involved in this is a  
18 building block. Just like some of you asked about a  
19 similarity to a pacemaker, pacemaker technology and  
20 all that we've learned about pacemakers and the  
21 difficulties are, indeed, the same in an implantable  
22 device. But just like a pacemaker is a building block  
23 for different therapies, the implantable Itrel  
24 stimulator is used in many, many therapies, all of  
25 which today are currently Class III, and many

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1       investigational things.

2               Now, the devices today is used for chronic  
3       pain. We know of some physicians who are -- I don't  
4       know what company conducting a study, but I know there  
5       are physicians conducting studies on peripheral nerve  
6       stimulation with this device. It's used in deep brain  
7       stimulation. Medtronic has an approval for tremor.  
8       We have a clinical going on in Parkinson's disease.

9               There are physicians -- I'm not sure if  
10       it's in the U.S. anymore -- but there are physicians  
11       who have been experimenting with deep brain  
12       stimulation for pain. There are studies going on in  
13       other countries for deep brain stimulation for  
14       epilepsy. There are many uses for this block.

15               So what you're being asked to do is not to  
16       down class a device today. You are being asked to  
17       take the entire range of things that this implantable  
18       pulse generator is used for and taking one of the  
19       indications and moving it into a different class.

20               We think this is going to be a little bit  
21       of a difficult compliance issue for FDA, and it's  
22       going to change the way devices are used, and I'll  
23       talk about some of the implications. But remember,  
24       you're only looking at a slice of the pie in this  
25       petition.

1 Here's another continuation. We have a  
2 clinical going on for gastrointestinal pacing. There  
3 is a urinary incontinence approval by Medtronic  
4 currently with other clinicals going on. There is a  
5 fecal incontinence clinical. People have used this  
6 for sleep apnea, for upper airway pacing. This is the  
7 same building block.

8 So if you move this device to different  
9 controls in 510(k) world, you are not looking at all  
10 of the indications. You're going to have the  
11 identical device controlled in two different manners.  
12 And I don't believe that's practical for an active  
13 implantable.

14 The pain issues can be quite complex,  
15 actually. Remember, we're only taking a small slice  
16 of even the pain situation here and talking about the  
17 indications that petitioner asked for. But there is  
18 many, many other pain issues that have always been  
19 treated as Class III issues, and the underlying  
20 devices Class III. Once again, you're going to have  
21 sort of a bureaucratic mess when you have all of these  
22 other indications retained as Class III and one slice  
23 cut out for a Class II.

24 So we'd like to now talk a little bit  
25 about the process, how something works through the PMA

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1 process. And please, please, please don't take this  
2 as an endorsement that all of the complexities of the  
3 modern PMA process are necessary in our opinion. We'd  
4 be glad to face simplification of them, and there is  
5 many ways to simplify them.

6 But we do not think that simply moving the  
7 Class II for this slice of this indication is an  
8 appropriate way to go at that. We should go at it for  
9 all of neurological devices if we do.

10 Now, there are many differences in the way  
11 PMAs are treated compared to Class II devices. And  
12 for active implantables, we still believe that this is  
13 the appropriate way. For example, all of the animal,  
14 bench, and clinical data review is much more rigorous.  
15 All of this is different in the PMA process from the  
16 510(k).

17 I don't think, in our opinion, standards  
18 have come to the point where it can replace all of  
19 that. And I should take a moment to talk about  
20 standards, since it was stated earlier that we are a  
21 participant of this standard. We're a big believer in  
22 standards. We like standards. We participate in  
23 them. We participated in this one.

24 The question is not whether standards are  
25 good but whether it is in itself a special control.

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1 Now, I know the Medtronic representatives on the  
2 Standards Committee, and it was never his intent that  
3 this standard become a special control.

4 We have spoken with the FDA representative  
5 -- this panel -- in the past, with I believe now  
6 retired Mr. Mumsner? Munsner. And his intent was  
7 that this not serve as a special control.

8 We have with us Dr. Richard North from  
9 Johns Hopkins who was on the committee that did that  
10 standard, and he says it was never intended to be a  
11 special control. Now, this standard has things in it  
12 to which everybody should comply. But in no way was  
13 it meant to be complete and a replacement for the rest  
14 of this process.

15 Standards are good, but they are not at  
16 the point where they are going to replace active  
17 implantable controls.

18 Second, manufacturing controls are  
19 reviewed in a different manner for Class II devices  
20 than they are for Class III Devices. The Advisory  
21 Panel oversight is different. Class III devices --  
22 the presumption is that they'll go to panel, unless  
23 the FDA can make a determination that you don't need  
24 to see it.

25 In Class II devices, the presumption is

1 that you won't see these devices in the future, unless  
2 the FDA makes a separate determination that one of  
3 them should come here. It's going to be a different  
4 view with less oversight from the panel.

5 Facility inspection is going to be  
6 different. This is one of the things that I wanted to  
7 talk -- you to understand about the ramifications of  
8 the action. It is not simply a question of the  
9 approval process. It's not a question of how the PMA  
10 is obtained rather than the 510(k). Once it falls in  
11 one of these classes, other things fall out.

12 As you all know, the FDA does not have the  
13 resources to inspect every facility as often as the  
14 statute requires. They just don't have enough people.  
15 It's a budgetary issue.

16 The FDA has established a risk position  
17 where it has determined certain classes of things that  
18 are inspected. And you do not have the same  
19 inspection on a Class II device as you do on a  
20 Class III device. Most Class II manufacturers are  
21 being, I think, on the average of something like five  
22 years inspected now, whereas the Class III  
23 manufacturers are getting their biannual inspections.

24 Additionally, there are inspection things  
25 built into the PMA process. Pre-PMA inspections are

1 done on PMA products. They are not done on 510(k)  
2 products. Post-PMA inspections are done on PMA  
3 products and not on Class II products under the  
4 system.

5 So this falls into different areas, and I  
6 want you to remember that this site -- this site, the  
7 other failed company, was discovered on a pre-PMA  
8 inspection. Now, we contend that this company would  
9 have been on the market under a 510(k) system. And I  
10 don't think there's a special control today for active  
11 implantables that I've seen that's going to take care  
12 of that issue.

13 This would have been on the market, would  
14 have been out there in patients, were it not for the  
15 PMA process.

16 Additionally, labeling is treated  
17 differently. We are talking here about indications  
18 and not devices, as I said. So the FDA labeling  
19 review is critical. The FDA has labeling authority  
20 for approval for PMA devices. It can review labeling  
21 for 510(k) devices but does not have the same  
22 statutory degree of control. So when you're talking  
23 about an indication shift, it matters how much control  
24 there is.

25 Now I'd like to talk a little bit about

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1 what happens after a PMA is granted. Once again, the  
2 difference between Class III and Class II has  
3 sequelae. The things that happen to the device after  
4 entrance in the market are different.

5 For example, now, PMAs require annual  
6 reports. This includes commonly a review of  
7 advertising, it's going to have adverse event  
8 reporting. There's going to be a number of things in  
9 there that are going to help the FDA determine how the  
10 device is performing. That is not done in 510(k)  
11 products.

12 Post-market studies -- this panel, for  
13 example -- I don't know if you individuals were on it,  
14 but the last time Medtronic was before this panel our  
15 neurological device got a recommendation that we have  
16 a post-market study. And post-market studies, in my  
17 experience, have become much more common for panels  
18 like you to ask for.

19 That process is going to be different than  
20 the 510(k) process because now the FDA can, in a PMA  
21 grant, require post-market studies. And there's going  
22 to be a different process.

23 The FDA's ability to -- in PMA grants to  
24 call these devices "restricted," which it has done for  
25 most Class III devices -- this has an effect on

1 labeling and advertising. For example, restricted  
2 devices have to have a brief statement of indications,  
3 warning, and contraindications in the ads. 510(k)  
4 products did not.

5 Actions you have to move this into  
6 Class II are going to fall through the waterfall  
7 events and end up in different advertizing controls.  
8 The difference between PMA supplements and additional  
9 510(k)s is also going to be different, and it will be  
10 a different process, which I think will have a  
11 different degree of control, and, once again,  
12 following on with the biannual inspections.

13 So there's a series of actions that are in  
14 place for PMA devices today that are going to go away.  
15 And it may not be obvious on just the Class change  
16 from III to II from the approval process, but it's --  
17 there's things after the approval process with which  
18 we're concerned.

19 And, once again, if you could wave your  
20 hands and make some of these regulatory obligations go  
21 away, you know, we'd be glad to participate in that  
22 process. But if so, it should be done with our eyes  
23 open on all uses of these Class III active devices and  
24 not this narrow use we're talking about.

25 So, and my conclusion is that you don't

1 have the information in front of you necessary to make  
2 your decision today. You don't have a fair view of  
3 what the adverse events were in the past. You don't  
4 have before you the history of the two companies that  
5 failed at this.

6 Petitioner, I'm sure, knew at least one of  
7 these companies and has chosen not to conclude that,  
8 and I -- I believe it's keeping you from knowing the  
9 history of this.

10 This is a difficult, difficult thing. And  
11 because we've been good at it and succeeded does not  
12 mean that the process was bad. I think it's an  
13 indication that things have worked well under this  
14 process and you should continue it.

15 Do I have any time?

16 CHAIRPERSON CANADY: Yes, you have about  
17 five minutes left.

18 MR. KLEPINSKI: I'd like to ask if we  
19 could -- if Dr. North could come up. Dr. Richard  
20 North is a well-known neurosurgeon and author from  
21 Johns Hopkins, who has implanted all of these devices  
22 and knows the history. And I'd like to give him an  
23 opportunity to offer his opinion on the down  
24 classification.

25 Dr. North?

1 DR. NORTH: Thank you.

2 Dr. Canady, ladies and gentlemen, I've  
3 been involved in this area since I was starting out in  
4 neuroscience and neurosurgery as a biomedical  
5 engineering post-doc in the early '70s.

6 And now, as a professor of neurosurgery at  
7 Johns Hopkins, I have a clinical practice very similar  
8 to Dr. Barolat's. And I share a number of his  
9 opinions and also research sponsors. Like him, I do  
10 research for both of these manufacturers.

11 I've been involved with the mechanical and  
12 electrical design, the systems engineering, the  
13 implantation, and clinical use of these devices, as  
14 well as their explantation. And that includes  
15 specifically the two devices referred to with internal  
16 batteries that are no longer available, and one which  
17 failed to make it to market. So I explanted some of  
18 the same devices that Dr. Barolat described.

19 I'm concerned as a clinician using these  
20 devices, and having patients referred to me who have  
21 them in place and who have problems, that the highest  
22 standards be followed. I'm concerned as a scientist  
23 that everything we do in the field be of highest  
24 quality.

25 And I'm concerned as one who has seen this

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1 field come a long way in the last 25 years that what  
2 is now a very safe and effective device, and that lets  
3 me do procedures as a clinician that are very  
4 gratifying, remain so.

5 It is the way it is because of excellent  
6 quality control on the part of manufacturers and on  
7 the part of regulatory bodies. And I think the PMA  
8 process has, in this sense, served us very well. So  
9 I'm just here to speak for continued excellent quality  
10 control on all fronts.

11 Thank you.

12 CHAIRPERSON CANADY: Thank you.

13 Panelists have any questions for Mr.  
14 Klepinski or Dr. North?

15 DR. HURST: I have one question.

16 CHAIRPERSON CANADY: Yes.

17 DR. HURST: This may be from the  
18 regulatory representatives standpoint. Did I  
19 understand that Medtronic is using the same device for  
20 the deep brain stimulation?

21 MR. KLEPINSKI: The IPG is the same, yes.

22 DR. HURST: Okay. I see.

23 CHAIRPERSON CANADY: Come to the  
24 microphone, please.

25 MR. KLEPINSKI: I can't answer technical

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1 questions if you get into the details, but the IPG  
2 itself is a building block. It's used for all of  
3 these various therapies.

4 DR. HURST: I understand.

5 MR. KLEPINSKI: And it's also used by  
6 physicians for their own research. Many physicians  
7 will try things that are off label. Occasionally,  
8 they'll have a patient that requires it and they'll  
9 use it for something off label. But they'll also do  
10 their own studies, get their own IDEs to study using  
11 the same building block with a different lead on to  
12 some other parts of the body.

13 I mean, literally, Medtronic is working  
14 from head to toe with this device. And all of those  
15 things are Class III currently. You know, the  
16 question I was concerned about is, when a physician  
17 could then -- who is going to do a clinical by the  
18 same device as a Class II device or the same device as  
19 a Class III, we would not have the same treatment,  
20 then, for the other investigational studies.

21 And I think that would be a very difficult  
22 thing to control, but it's the same building block.

23 CHAIRPERSON CANADY: Other questions for  
24 the representatives of Medtronic?

25 We're going to close that portion of the

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1 meeting now and go to the open panel discussion. Dr.  
2 Edmondson has reviewed this topic for the panel and  
3 has a presentation.

4 DR. EDMONDSON: Okay. Thank you, Dr.  
5 Canady.

6 The presentations from the petitioners and  
7 the protester is enlightening, and I mean that  
8 sincerely. And in that context, my position and task  
9 here is to speak from the mind's eye of a treating  
10 physician, one who has seen patients with chronic pain  
11 and who have had an opportunity over the past 10 years -  
12 or so to observe these devices used for intractable  
13 pain.

14 Let me start with really how this came  
15 about, how the -- what -- how the rationale for using  
16 neuromodulatory stimulation for pain control came  
17 about. And this was borne from, really, theory --  
18 theory presented by Melzack and Wall in 1965, the Gate  
19 Control Theory.

20 And in this theory, based upon  
21 neurophysiological animal data, Melzack and Wall  
22 devised a -- proposed a theory in which they outlined  
23 that A-fibers, when stimulated, can block the  
24 conduction of C-fibers or inhibit the input that  
25 C-fibers would make to the cells in the spinal cord

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1 that goes to pain centers and tells the brain that  
2 pain is occurring.

3 Since the inception of these devices for  
4 use in the clinical arena in 1967, research has  
5 demonstrated that stimulation along the dorsal column  
6 can influence a number of different processes in the  
7 spinal cord, including the release of  
8 neurotransmitters, GABA, the reduction of excitatory  
9 amino acids, and, in fact, potentially the direct  
10 blockade of C-fiber conduction based upon direct  
11 interference from the stimulation itself, rather than  
12 through A-fibers.

13 The point of this is that theory brought  
14 us to this technology, and that theory has also  
15 brought us to the notion of the more you know, the  
16 more you don't know. And we have learned through this  
17 that the processes are very complex.

18 But the bottom line is that over time it  
19 has been observed that spinal cord stimulation can  
20 provide relief in a number of different clinical  
21 scenarios. We're asked to look at the indication for  
22 chronic pain. The literature is really robust for a  
23 number of other indications, such as peripheral  
24 vascular disease, angina pectoris. There is a lot of  
25 European literature regarding these entities.

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1           There is also some literature for movement  
2 disorders and spasticity, although with really mixed  
3 reviews.

4           Now, in the context of trying to discern  
5 risk and class reclassification, and that sort of  
6 thing, I'd like to revisit that after we have looked  
7 and reexamined some of the data that you have heard  
8 about from our previous presenters.

9           I've had an opportunity to review a small  
10 portion of articles, namely about 35 articles out of  
11 perhaps over 200 articles that are known to be out-  
12 there, addressing how these stimulators are used, what  
13 the efficacy is, and cited risk.

14           Now, of these studies, I call your  
15 attention to Boggi, et al., an Italian study, where  
16 over 400 patients entered the study, and 363 received  
17 spinal cord stimulation. The vast majority of these  
18 patients had either back pain or RSD.

19           The point here -- and I'm not going to go  
20 through reading all of these iterations of different  
21 responses in risk -- but initially, the response is  
22 roughly, in this study anyhow, 87 percent of the  
23 patients had pain relief immediately. Two years  
24 later, 58 percent had relief.

25           The other articles cited in the summary

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1 provided to you, my colleagues on the panel -- without  
2 going through them individually, I should underscore  
3 that in my own practice, in collaboration with  
4 Neurosurgeon, that we have found also an attrition  
5 over a period of two to five years from anywhere from  
6 75 percent response rate -- with pain relief greater  
7 than 50 percent -- dropping to about 60 percent.

8           Nonetheless, even in patients who report  
9 that they get less than 50 percent relief, they are  
10 unwilling to turn the stimulator off or have it  
11 explanted. So, obviously, in that context some folks,  
12 even though they don't meet criteria for relief, which  
13 is 50 percent or better, are experiencing some benefit  
14 and would rather have the stimulator in place.

15           Now, with regard to risks, it varies  
16 significantly in terms of data in the Eighties versus  
17 data in the Nineties. It also varies according to the  
18 series because some of these series had only 40  
19 patients, others had 70, some, a little over 100. The  
20 vast majority of publications are really within that  
21 range. Very few are several hundred.

22           Now, the most common complication is lead  
23 migration or dislodgement and that is the reason for  
24 loss of pain relief.

25           With unipolar leads, this generally means

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1 that you have to go back and reposition them.

2 With leads that have several electrodes,  
3 on the other hand, with reprogramming, the incidence  
4 of having to go back and do another surgery to  
5 reposition these leads, is reduced.

6 Likewise, for the octrode electrode,  
7 namely with eight electrodes on each lead that is  
8 available in the external system, the use of  
9 reprogramming has actually greatly reduced the need to  
10 reposition those leads because you have several  
11 different permutations to work with to salvage the  
12 loss of coverage for pain relief.

13 But we are still faced with some  
14 malfunctions that can be quite striking.

15 However low the incidence might seem, on  
16 a personal level and attempting to reprogram the  
17 simulators and dealing with individual cases, we are  
18 again reminded of the complexities of all of these  
19 devices and how glitches in programming, circuitry or  
20 whatever it might be, can be multiplied.

21 The incidence of infection roughly, in  
22 most series, is two to three per cent. In earlier  
23 years it was relatively higher in some instances  
24 because some leads were placed intradurally, some  
25 patients had multiple attempts because of epidural

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1 fibrosis. The incidence rate for complication for  
2 those patients is higher.

3 Curiously, it is within patients who has  
4 had numerous surgeries, more than two, to rectify the  
5 problem.

6 So, that is jut to give you the idea of  
7 total numbers of what that reflects.

8 Now, basically the efficacy of these  
9 devices is well-established and that is why the  
10 currently existing ones are FDA-approved and really  
11 have the FDA stamp of approval with the internal-  
12 device being a class III.

13 Now, I call your attention, my fellow  
14 panel members, to the last page of my handout.

15 Really, the crux of our deliberation is  
16 whether or not the existing body of evidence in the  
17 literature is sufficient to justify reclassification.

18 We have over 250 articles, most of which  
19 are case studies. We are dealing with currently  
20 available effective devices that have comparable risk.  
21 But I call your attention to a couple of nuances.

22 Recently I had a patient whose stimulator  
23 would sporadically turn on and cause electric jolts.  
24 I think in part because it was near the end of the  
25 battery life.

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1 But in any event, attempts at adjusting  
2 the stimulator inadvertently caused an increase in the  
3 intensity of stimulation and that person could not  
4 turn it off.

5 So, ultimately, that required explanation  
6 to rectify the situation.

7 Although this is not a commonly  
8 experienced complication, new circuitries, the fusion  
9 of existing circuits, batteries and other components,  
10 in that setting we have to ask whether or not  
11 combining these modular components into one is equal  
12 in effectiveness with the same degree of risk.

13 Basically, I would just like to stop there  
14 and open to the rest of the panel for discussion.

15 CHAIRPERSON CANADY: Thank you. As we  
16 have the general conversation, just so you know, Dr.  
17 is going to start putting the questions up for us, so  
18 don't get distracted by that.

19 General comments?

20 Dr. Walker?

21 DR. WALKER: Since some of these  
22 engineering issues, I don't mind going next.

23 We have heard there were two firms who had  
24 pre-market approval for implanted pulse generators and  
25 in fact there were two companies that worked under

1 IDEs, one of which worked very successfully but  
2 decided there was no market potential, and made a very  
3 safe product that was very good.

4 We used those at our institutions in the  
5 early Eighties. But Medtronic came out with one that  
6 was programmable and this one was not programmable so  
7 that firm left the market.

8 So, to set the record straight, only  
9 Medtronic can make a proper IPG. Other companies have  
10 made them, but Medtronic has made them with more bells  
11 and whistles and the market demanded bells and  
12 whistles.

13 In the early Eighties when we started  
14 working with these, the issues were battery life and  
15 integrity of the hermetic seal surrounding the  
16 titanium case.

17 In the almost 20 years that have ensued,  
18 my opinion as an engineer is that the technology has  
19 improved and these are no longer the cutting edge  
20 problems that they were in the early Eighties when the  
21 two devices that received PMA came out.

22 The question that we need to look at is  
23 whether we still need a high level of pre-market  
24 scrutiny for implanted pulse generators now that the  
25 most common failure modes are external to the

1 implanted pulse generator.

2 The most common failure modes are lead  
3 migration, lead wire breakage, electrode migration,  
4 and those aren't parts of the building blocks that we  
5 are talking about today.

6 The petition that Medtronic reviewed  
7 points out a lot of things that have gone wrong under  
8 class III regulation.

9 I didn't hear the part that if all these  
10 bad things happened under class III, why wouldn't they  
11 happen under class II?

12 I didn't hear that.

13 I did hear, and have a question for FDA  
14 about this, that class II manufacturers are only  
15 inspected once every 5 years. Is that true?

16 MR. DILLARD: Jim Dillard. I guess I need  
17 to make a comment on that.

18 While I am not from the Office of  
19 Compliance I need to give a little bit of background  
20 that, with the resource crunch we are currently under,  
21 much of what we are doing is prioritizing the kind of  
22 manufacturers that we inspect and how often we inspect  
23 them.

24 Irrespective of whether or not it is class  
25 II or class III, those high risk, implantable kinds of

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1 products tend to get more scrutiny and tend to be  
2 inspected more often, too. That is without regard to  
3 whether they are class II or class III.

4 Now, the reality of the inspection  
5 situation of all of the class II devices -- now we  
6 will take out class III because class III has pre-  
7 inspection, post-approval inspection, the types of  
8 things that Medtronic spoke about.

9 In the class II regime is a hierarchy of  
10 how often something will get inspected. There are a  
11 number of factors that go into it.

12 The reality of it is unless you are in one  
13 of the high categories that we tend try to inspect  
14 more often, if you are in either a middle or lower  
15 tier in terms of risk, reports, how many failures you  
16 have been having, a number of things could kick it up  
17 into the higher category, a lot of times the  
18 inspections are happening every four to five years, on  
19 average.

20 So, just because this product type, if it  
21 were down-classified to class II, there are a number  
22 of things with any individual manufacturer that might  
23 cause them to be inspected more often.

24 So, I wouldn't call it a general rule, but  
25 I would say that the class II types of products are

1 being inspected much less frequently than class III  
2 products.

3 DR. WALKER: Would we include as a special  
4 control the same by-annual inspection that other  
5 implanted pulse generator manufacturers were subjected  
6 to?

7 MR. DILLARD: I believe that if you think  
8 that is important that you could put that in as  
9 recommendation, yes.

10 CHAIRPERSON CANADY: Other questions in  
11 general discussion? —

12 Then we are going to begin our question-  
13 by-question discussion.

14 Question one is up, I believe.

15 Dr. Gonzales, maybe we will go the other  
16 way around and give Dr. Hurst a break for being the  
17 first guy on Wednesday.

18 DR. GONZALES: Well, the first part of the  
19 question, "Do you believe there are any other  
20 additional risk to health other than those identified  
21 in the petition," I do have a concern that using the  
22 statistics that ANS has presented when they talked  
23 about the MDR incident reports, 25 per cent of the 400  
24 plus MDRs were in the "Other" category.

25 So, the real question is, is 25 per cent

1 "Other" enough of a safety issue if those other  
2 incidents were in fact significant enough to be a  
3 safety issue for the patient.

4 So, I have a real question about the  
5 unknown 25 per cent "Others" that have been occurring.

6 Until that 25 per cent is better  
7 explained, and that is talking about the 400 plus  
8 rather than the 700 reports that may also possible, I  
9 am concerned about that.

10 Are there additional risks? I just can't  
11 answer that. I am not sure we have enough  
12 information. That is the first part of the question.

13 The second part of question one, "Please  
14 include in your discussion whether class III totally  
15 implantable spinal cord stimulator devices is utilized  
16 by the same population as class II radio frequencies  
17 coupled SCS device?"

18 Right now it does not appear that the  
19 implanted pulse generator population is less or more  
20 complex as far as the patient selection.

21 So, it does not appear that there is a  
22 difference.

23 There are differences though in terms of  
24 patient effects that have not been stated. I am not  
25 sure that they are that significant, but they could

1 be.

2 For instance, with the radio frequency,  
3 tactile stimulation occurs with the placement of the  
4 external radio frequency device that, with tactile  
5 stimulation, was some of the indication of pain.

6 Since the device has to be placed directly  
7 on the skin in roughly the TAT 10 dermatone, there are  
8 pain states such as reflex sympathetic dystrophy  
9 arachnoiditis and spinal cord central pain where the  
10 pain can actually spread.

11 This can happen spontaneously over time  
12 regardless of the stimulation. Therefore, radio  
13 frequency contact could in fact influence.

14 But other than that, which is responding  
15 more to the inspect than the implantable, I don't  
16 think there were many major differences in the  
17 patients.

18 You could speculate to that because it  
19 requires more attention that the psychologically  
20 impaired individual who should be screened out to  
21 begin with might be a more complex patient.

22 So, I don't believe there is a difference  
23 in complexity, looking at it overall.

24 CHAIRPERSON CANADY: Dr. Gatsonis?

25 DR. CONSTANTINE: Based on the universe of

1 information we have received, it is difficult to  
2 answer this question. I don't see any reference, one  
3 way or the other, to this.

4 What we know about implanted pulse  
5 generators is based apparently on one IPG which is out  
6 on the market.

7 So, I don't think you can make a case or  
8 a prediction about how a different implanted pulse  
9 generator made by a different company would operate.

10 So, there may be additional risks that  
11 don't apply to all the IPGs, but they apply to  
12 specific ones.

13 CHAIRPERSON CANADY: Ms. Maher?

14 MS. MAHER: I don't have any comment.

15 CHAIRPERSON CANADY: Dr. Walker?

16 DR. WALKER: On the first question there  
17 are no additional risks. I think ANS has done a good  
18 job of identifying them.

19 For the second part of the question, for  
20 this indication, it is the same patient population.  
21 I think we need to be very specific about that because  
22 the Itrel, being such a wonderful universal device, is  
23 being used for other indications and applications as  
24 well.

25 For the third question, "Are the risks

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1 unique to the class III population?"

2 The only unique risk is the greater  
3 difficulty turning off runaway stimulation, but we  
4 haven't seen a great number of reports of runaway  
5 stimulation with implanted pulse generators which are  
6 more easily stopped with the RF system.

7 CHAIRPERSON CANADY: Dr. Ku?

8 DR. KU: No additional comments.

9 CHAIRPERSON CANADY: Ms. Wojner?

10 MS. WOJNER: No additional comments.

11 CHAIRPERSON CANADY: Any other comments?

12 Dr. Edmondson?

13 DR. EDMONDSON: Yes. Basically, the  
14 population for both types of stimulation, RF or  
15 totally implanted are the same.

16 But there is one qualifier.

17 Patients with primarily back pain,  
18 midline, truncal pain, appear to do better with  
19 programs that offer several modalities and multiple  
20 leads.

21 So, the matrix system, the other system  
22 with eight leads, you can put two different stimulator  
23 leads on with eight electrodes each, those seem to  
24 offer an advantage.

25 The external system seem to offer an

1 advantage to selected patients who have primarily  
2 truncal pain rather than limb pain.

3 But generally, for both devices, if you  
4 have limb pain you are more likely to have relief for  
5 the long haul than those who have midline pain.

6 With regard to risk, I think it is already  
7 stated and addressed. There are no additional risks.

8 Class III, I should mention, if you have  
9 disagreeable stimulation, an implanted pulse generator  
10 that isn't working, a failed battery or whatever it  
11 might be, you just take the strap off and you are all-  
12 set.

13 A brand new system with all its nuances  
14 may have some problems that would require an incision,  
15 so that has to be taken into account.

16 CHAIRPERSON CANADY: Dr. Hurst?

17 DR. HURST: Nothing additional.

18 CHAIRPERSON CANADY: Any other general  
19 comments regarding question one?

20 We could have question two?

21 Dr. Gonzales?

22 DR. GONZALES: "For all of the risks to  
23 health identified by the sponsor, are the proposed  
24 special controls adequate?"

25 The issues come down to really the

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1 abnormal stimulation that may occur, the battery  
2 running out and the replacement of the battery.

3 And finally, the concerns that have been  
4 brought up about manufacturing.

5 Regarding the manufacturing, I can't  
6 address that. I think there are other people here who  
7 are experts and can address that.

8 As far as the abnormal stimulation and the  
9 battery running out, this is placed into and known  
10 ahead of time, and patients are warned that this is  
11 part of the problems or risks associated with this  
12 particular stimulator type.

13 So, it comes down to the risks of the  
14 surgery and repeat surgery, and does that warrant the  
15 class III versus the class II.

16 I think those have been discussed and  
17 identified and I don't think at this point in time,  
18 special controls other than those that have already  
19 been identified, are really necessary.

20 CHAIRPERSON CANADY: Dr. Gatsonis?

21 DR. GATSONIS: No additional comments.

22 CHAIRPERSON CANADY: Ms. Maher?

23 MS. MAHER: Yes. I'd just like to make at  
24 least one comment on the FDA inspection issue that  
25 came up earlier.

1           The law has not changed. The FDA is  
2 supposed to inspect all facilities every two years.  
3 It doesn't happen and they have turned to more of a  
4 risk-based method of looking at things.

5           But, in fact, all manufacturers are still  
6 required to comply with the quality system  
7 regulations.

8           Many different things generate inspections  
9 and the rate of inspection is really related to where  
10 your facility is located and how busy the division is  
11 that is there, as to anything else.

12           So, I think that we need to be aware that  
13 we need to follow the manufacturing regulations as to  
14 how we make our product and there are a lot  
15 regulations on us to do that.

16           CHAIRPERSON CANADY: Dr. Walker?

17           DR. WALKER: As I reviewed the proposed  
18 labeling and special controls from ANS, unfortunately  
19 I found many shortcomings and I kind of hate to get us  
20 into the business of word-smithing on Friday  
21 afternoon.

22           So, I thought what I would like to do is  
23 make a film of the problems that I have and maybe we  
24 could go through them. Is that okay?

25           CHAIRPERSON CANADY: If you use the

1 microphone, Dr. Walker.

2 DR. WALKER: Okay. The first one, the  
3 place where we are looking is in the ANS petition,  
4 page 17, section D.

5 One of the proposed labels they include is  
6 the phrase, "Adverse events include undesirable  
7 changes in stimulation." It seems to me if this is  
8 going into a patient or physician booklet, it seems a  
9 little bit vague and needs a little bit of elaboration  
10 as to just what undesirable changes in stimulation  
11 means.

12 What I would like to suggest is that we  
13 point that out to the FDA staff and perhaps suggest  
14 that they work with the sponsor or the ANS to get that  
15 changed rather than we word-smith it here on Friday  
16 afternoon.

17 What is the procedure? Do I go through  
18 them one at a time? How do you want to do it?

19 CHAIRPERSON CANADY: I would go through  
20 them all at once.

21 DR. WALKER: Go through them all? Fine.

22 The second one, section E, the original  
23 wording is "adverse events include possible pain at  
24 the implant sites" since there is both and electrode  
25 implant site and a pulse generator implant site.

1 I think that should be tightened up to  
2 indicate that the pain is at the pulse generator  
3 implant site perhaps due to anode break excitation or  
4 some phenomenon like that.

5 At section F there is a phrase "adverse  
6 effects include allergic response". This is the  
7 section on biomaterials and I suggest we include the  
8 phrase "to the materials used in the device."

9 Then in the section on other adverse  
10 events, these include erosion and erosion, again, seem  
11 pretty broad. We might want to consider saying skin-  
12 erosion over the site of implantation rather than just  
13 the more broad phrase, erosion.

14 CHAIRPERSON CANADY: Any other comments  
15 you would like to make?

16 DR. WALKER: Do we want to talk about  
17 including, as well, something about inspections and  
18 annual reports?

19 CHAIRPERSON CANADY: I think that is very  
20 reasonable to discuss at this time.

21 DR. WALKER: That's it.

22 CHAIRPERSON CANADY: Dr. Ku?

23 DR. KU: I think we pretty much agree that  
24 spinal stimulation works, so that isn't a issue for  
25 me.

1           The main question is, is the power device,  
2           whether it is inside the body or outside the body, and  
3           it seems to be more of an engineering question,  
4           whether manufacturers can reliably and with the  
5           ability to repetitively produce devices that don't  
6           fail. That is the bottom line.

7           The question is whether or not the current  
8           regulatory procedures regarding good manufacturing  
9           practices and inspections to be sure those practices  
10          are followed, as well as proper design of the  
11          circuitry so that it is designed not to fail or has  
12          been tested adequately so that all the bugs have been  
13          worked out, whether or not the programming has been  
14          tested, seems to be the main question.

15          And I am a little unclear what the current  
16          state of the art is regarding the materials. Could  
17          you address that?

18          DR. WALKER: In terms of biocompatibility?

19          DR. KU: Biocompatibility, whether or not  
20          it is very difficult to design a system that is  
21          relatively fail safe, or it just takes a bunch of  
22          smart engineers to work real hard to do it?

23          DR. WALKER: At the risk of sounding  
24          facetious, good engineers who work real hard can do  
25          almost anything.

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1 Having said that, the basic materials, and  
2 of course we don't know what ANS is proposing to use  
3 as their materials, but assuming it is similar  
4 materials to Medtronic which is titanium case or a  
5 urethane or plastic coated lead, those materials have  
6 been around for 25-30 years and seem to be fairly  
7 stable.

8 With respect to reliability certainly  
9 there have been even RF coupled systems, particularly  
10 the frenetic nerve simulators and the cochlear  
11 prosthesis have achieved tremendously high degrees of  
12 reliability.

13 I am not concerned about whether or not  
14 that is theoretically possible and it would be left to  
15 design controls that would be imposed on ANS to be  
16 sure that they achieved the same high degree of  
17 reliability that other people in this business have  
18 achieved.

19 CHAIRPERSON CANADY: Ms. Maher?

20 MS. MAHER: I'd just like to remind people  
21 again that we are not talking about the approveability  
22 or the non-approveability of the ANS product, but  
23 whether these devices fit the criteria for a class II  
24 device rather than a class III device.

25 So, I think we need to be very careful in

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1       how we look at this and how we discuss this.

2               DR. KU: Right. We are mainly looking at  
3       spinal stimulation.

4               CHAIRPERSON CANADY: Any other comments,  
5       Dr. Ku?

6               DR. KU: No.

7               CHAIRPERSON CANADY: Ms. Wojner?

8               MS. WOJNER: I am basically pretty  
9       comfortable with the information that has been  
10      presented.

11              I think the points that Ms. Maher has-  
12      brought up are right on target.

13              CHAIRPERSON CANADY: Dr. Edmondson?

14              DR. EDMONDSON: Having said that, I think  
15      I am somewhere in between.

16              My uneasiness relates to probably more the  
17      bells, whistles and engineering and the assurance that  
18      really external versus internal pulse generators,  
19      whether or not that distinction is a critical one,  
20      because of the safety of removal of the device.

21              An internal device would require an  
22      incision and removal in the event of malfunction.

23              Currently available simulators have  
24      demonstrated rather low incidence of pulse generators  
25      problems and circuitry and software problems.

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1                   Nevertheless, in this milieu of providing  
2 a competitive advantage, that is what has made these  
3 two companies survive thus far.

4                   Each time we redesign and create new  
5 software and programming, there are nuances that may  
6 be unforeseen.

7                   CHAIRPERSON CANADY: Dr. Hurst?

8                   DR. HURST: I have no comments.

9                   CHAIRPERSON CANADY: Any general comments  
10 about question two?

11                   Question three?

12                   DR. GONZALES: "Does the information in  
13 the petition and your professional experience support  
14 reclassification of the device?"

15                   I'll bring up the question I have again of  
16 the 25 per cent "Other" group.

17                   This may be enough to question the safety,  
18 if those 25 per cent MDRs were related to battery  
19 failure, battery problems, power generator.

20                   So, I would also ask Dr. Gatsonis,  
21 statistically, since that is your expertise, the kind  
22 of numbers, the 25 per cent, is that of concern to  
23 you?

24                   DR. GATSONIS: Well, there is no  
25 denominator in the data so it is very difficult to

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1 know what they represent.

2 Yes, I don't think anybody has any idea  
3 whether this is a large number or a small number  
4 compared to all the implants that were made.

5 The only thing that you could do with that  
6 data is compare IPGs to the relative rates within IPGs  
7 to within RF. But we don't have those.

8 We don't have any data for this  
9 discussion. It is somewhat bizarre.

10 DR. GONZALES: And unfortunately, that's  
11 the crux of the problem right now. —

12 As long as there is a question of 25 per  
13 cent of the MDRs being "Others" that may involve  
14 battery or distinguish this from radio frequency it is  
15 a concern.

16 I don't know how to respond either.

17 It may be from the manufacturing, the  
18 abnormal stimulation runout, the replacement, all of  
19 that appears to be an acceptable aspect of the  
20 implantable that is controllable in such a way that  
21 a class II is appropriate.

22 I still have the one question about the 25  
23 per cent and if those are in fact related to battery  
24 function. That hasn't come out.

25 I can't answer that question without more

1 information on the 25 per cent.

2 CHAIRPERSON CANADY: Dr. Gatsonis, other  
3 comments?

4 DR. GATSONIS: Based on the information of  
5 the petition, I cannot really think that this  
6 reclassification should go ahead.

7 I don't see that there is enough evidence  
8 to support this. And unless the evidence is there, I  
9 am ready to be swayed by the argument that there are  
10 a lot of implantable devices out there that look very  
11 similar to this and they are all in the third-  
12 category.

13 I don't see why we would take one  
14 particular one and move it this way, in the absence of  
15 data and the absence of that kind of convincing  
16 information.

17 So, until that is done, and those devices  
18 are looked at more generically, I don't see why, in  
19 this specific case, we need to move it.

20 CHAIRPERSON CANADY: Ms. Maher?

21 MS. MAHER: Yes. I think what this  
22 question is asking, and I actually, from experience of  
23 course, can't answer that, being a lawyer not an MD.

24 But I think what we are looking at, the  
25 law asks this panel and the FDA to use the least

1 burdensome possible way to get products on the market  
2 for their intended use.

3 So, you can pull it out, if in your  
4 professional opinion spinal cord stimulation for this  
5 intended use falls in the class II, then it is  
6 perfectly okay.

7 I think this panel needs to evaluate what  
8 you know about spinal cord stimulation as a whole.

9 CHAIRPERSON CANADY: Dr. Walker?

10 DR. WALKER: In general, I agree with  
11 Sally.

12 Our job is to look at what is the lowest  
13 classification that will still provide reasonable  
14 safety and effectiveness.

15 I believe that is class II.

16 I am not bothered by the fact that there  
17 would still be some class III indications, deep brain  
18 stimulation for example, because that is a newer  
19 application and not as time tested and proven as  
20 spinal cord stimulation is.

21 This is not a life support application,  
22 either.

23 My one remaining area of concern that  
24 still remains is why pacers are all class III?

25 These devices are being proposed for class

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1 II when they share, essentially, the same technology.

2 If the reason pacers are still class III  
3 is just because they are life support, then I am  
4 comfortable moving this to II.

5 But if there is a technical reasons why  
6 pacers are still class III as well, then perhaps this  
7 should remain in class III and maybe someone from FDA  
8 could answer that question.

9 CHAIRPERSON CANADY: Mr. Dillard? You are  
10 the lucky one.

11 MR. DILLARD: Jim Dillard, I get all the  
12 tough ones.

13 One of the significant differences, Dr.  
14 Walker, that you bring up between the two, and I would  
15 have to agree, is that one is life supporting and the  
16 use for the other product is not life supporting.

17 One other thing I might clarify a little  
18 bit, too, because one of the issues that was brought  
19 up by one of the presenters was that specifically you  
20 all are looking for an indication for use and I need  
21 to provide just a little clarification on that,  
22 because we at FDA define a medical device as the  
23 article plus what it is intended to do.

24 We can't separate those two. So, when we  
25 talk about anything we classify, anything you see in

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1 our Code of Federal Regulations, it includes a product  
2 description of the article and an intended use.

3 So, we can't separate those.

4 So, in this case we are asking for a  
5 specific situation for a product and how it is  
6 intended to be used. Is there enough information to  
7 support reclassification; that is what the petition is  
8 about, and then what are the level of controls that  
9 can reasonably control for the safety and  
10 effectiveness of the product..

11 That is what I think the legal obligation—  
12 is.

13 So, whether or not, Dr. Walker, there is  
14 anything else other than the fact that there is a  
15 significant difference between one is life supporting  
16 and one is not life supporting, I don't think that we  
17 have gone into the detail to describe between the two,  
18 because again, I think my point of this device, how it  
19 is used, the data that is available for this device  
20 and this use, is the standard by which we judge  
21 reclassification.

22 Not compared to where other products with  
23 other indications might be based on their known  
24 information, the knowledge of the product and their  
25 intended use.

1 CHAIRPERSON CANADY: Other comments, Dr.  
2 Walker?

3 Dr. Ku?

4 DR. KU: I'm pretty convinced that the  
5 indication as far as spinal stimulation is a good one  
6 that works.

7 The part that really bothers me about this  
8 petition is I don't think they have shown the data  
9 that would make it possible to easily and reliably to  
10 produce a component that would have a low failure  
11 rate.

12 If that can be done, as Dr. Walker  
13 suggests, relatively easily, then I think it is quite  
14 reasonable because it is just an engineering issue.

15 And if you can, with regular manufacturing  
16 controls, assure that the failure rate of this product  
17 is going to be low, then I don't have a problem with  
18 that.

19 But on the available data that is  
20 presented in the petition itself, I don't have that  
21 evidence.

22 CHAIRPERSON CANADY: Ms. Wojner?

23 MS. WOJNER: It is getting tougher.

24 I think a lot of my thoughts have been  
25 represented.

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1 I think Mr. Dillard's comments were  
2 extremely helpful because being able to look at this  
3 within those brackets proposed by ANS provides me a  
4 lot more comfort to say that this could potentially  
5 fit within the realm of a class II.

6 CHAIRPERSON CANADY: Dr. Edmondson?

7 DR. EDMONDSON: I think I would echo Dr.  
8 Ku's comment that largely it pivots around the whole  
9 engineering issue because I think there are enough  
10 special controls there.

11 But given current technology is there  
12 enough quality assurance, after going through those  
13 hoops of special control, that would assure that this  
14 would be a relatively safe new device, totally  
15 implanted.

16 CHAIRPERSON CANADY: Dr. Hurst?

17 DR. HURST: I agree with Mr. Dillard's  
18 remarks.

19 When we are talking about a device as well  
20 as well as an indication that's linked, I think that  
21 is a very important concept, at least for me, to keep  
22 in mind.

23 I think that the special controls that we  
24 have discussed already seem to be something that we  
25 can make very stringent, if we need to.

1 I have a lot of faith in the ability of  
2 these special controls to maintain relatively high  
3 standards of safety and efficiency.

4 I think based on that, and the fact that  
5 we are talking about a device and an indication, I  
6 think I could lean towards putting this into class II.

7 CHAIRPERSON CANADY: Any other general  
8 comments about question three?

9 Then we move on to the final question,  
10 question four.

11 DR. GONZALES: "If you believe that the  
12 class III spinal cord stimulator device should be  
13 reclassified to a class II device, please discuss the  
14 appropriate indications for use for the totally  
15 implanted spinal cord stimulator device."

16 I do not believe there should be  
17 reclassification from a class III to a class II device  
18 because of my concern regarding the safety issue and  
19 the unknown regarding the MDRs that have already been  
20 brought out.

21 CHAIRPERSON CANADY: Dr. Gatsonis?

22 DR. GATSONIS: I think the  
23 reclassification should go ahead.

24 CHAIRPERSON CANADY: Ms. Maher?

25 MS. MAHER: No comment.

1 CHAIRPERSON CANADY: Dr. Walker?

2 DR. WALKER: I believe we can reclassify  
3 it and with the fairly tightly defined and limited  
4 indication that has been proposed is appropriate.

5 CHAIRPERSON CANADY: Dr. Ku?

6 DR. KU: I agree with Dr. Walker. I am a  
7 little disappointed that the petitioner has not  
8 presented the data to show that it is easy or reliably  
9 possible through standard manufacturing to achieve  
10 these conditions of reliability. I think they should  
11 have done that.

12 CHAIRPERSON CANADY: Ms. Wojner?

13 MS. WOJNER: No additional comment.

14 CHAIRPERSON CANADY: Dr. Edmondson?

15 DR. EDMONDSON: If I could stay in  
16 suspension for a little while and perhaps the FDA  
17 could help me out a little bit.

18 CHAIRPERSON CANADY: Well, we are going to  
19 have a session here for clarification.

20 Obviously, there are some questions that  
21 I would clarify if I were these people.

22 Dr. Hurst?

23 DR. HURST: No additional comment.

24 CHAIRPERSON CANADY: Any other general  
25 comments regarding question four?

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1 If not we are going to offer the  
2 opportunity for the presenters to clarify issues.

3 We will start with Dr. Johnson.

4 If you have any comments you would like to  
5 make?

6 MR. JOHNSON: Thanks again. Drew Johnson;  
7 you all know me by now.

8 Just a couple of quick comments regarding  
9 the opposition's concerns, and they do make a fine  
10 product and I do believe that, given the opportunity  
11 for reclassification, given the controls that we have  
12 proposed, given the FDA and their ability to choose  
13 whether or not a device goes to market or not, I think  
14 that this device should be reclassified.

15 But I had some problems with a couple of  
16 things regarding manufacturing and reliability of  
17 devices and so forth.

18 And I do believe that the use of special  
19 controls and the use of risk assessment to come up  
20 with technological answers to questions, and I think  
21 they have already been answered, like the runaway  
22 stimulation situation. Magnets are now available. A  
23 simple switch turns off the device.

24 So, that is all I have to say.

25 CHAIRPERSON CANADY: Mr. Klepinski?

1 MR. KLEPINSKI: I still think that the key  
2 issue under this is what has been hinted at from this  
3 side of the table, and has never been addressed.

4 The issue has been talked around, but  
5 never addressed.

6 There is nothing in the petition that  
7 addresses the difference of going from an implantable  
8 and the risks involved in designing an implantable and  
9 the risks of controlling it through RF.

10 Dr. Walker said this is an engineering  
11 change and is workable.

12 We agree that we have done this. It is  
13 possible. But it has been done under a quality  
14 control scheme that is quite complex, closely  
15 controlled by the FDA.

16 The success in doing that under the  
17 current system does not mean that it is going to fall  
18 in place automatically for everybody.

19 I contend that active implantables from  
20 other devices.

21 That is why, in the European system,  
22 active implantables are controlled under a different  
23 directive than the rest of medical devices.

24 That is what we are talking about today.  
25 Not the effect of the lead in the spine, all the talk

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1 has been about the therapy.

2 We'll say the therapy is generally the  
3 same, the contact with the spine, the same. The  
4 difference is between an active implantable and an  
5 inactive implantable.

6 There is nothing in the petition that  
7 talks about any specific special controls that are  
8 going to deal with active implantables, as far as the  
9 manufacturing.

10 In Europe, when these are controlled, this  
11 ANSI standard is not used as the standard for under-  
12 the CE mark.

13 Actives are treated differently and  
14 inspected differently.

15 In the United States, active devices have  
16 always been class III. To the best of my knowledge,  
17 this would be the first implantable moved into class  
18 II.

19 Now, this may be the wave of the future  
20 and you are going to move all of these various  
21 neurological therapies down.

22 But I do not think that you have in front  
23 of you the information needed to fulfill your  
24 statutory obligation.

25 That is, the statute says you move these

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1 into class II if you have adequate special controls.

2 The special controls that are shown here  
3 talk about EMF interference.

4 They talk about whether your microwave is  
5 going to interfere or a theft detector, they talk  
6 about labeling.

7 But they do not talk about the  
8 manufacturing and testing of active implantables.

9 So, that information is not here and I  
10 don't think that, in the absence of it --

11 I don't want to sound like I know more  
12 than you about the manufacturing of pacemakers; we  
13 have experts that do that.

14 I don't want to make it sound like there  
15 is black magic here.

16 But I want you to understand that the  
17 whole system that is protecting the active  
18 implantables is different from the controls that you  
19 see in these.

20 You can't simply go out of here saying  
21 that you will throw a few more things into the special  
22 controls and take care of the whole rest of the PMA  
23 scheme. There is a major difference here.

24 When we talk about runaway is not a  
25 problem anymore. That is because we worked at this

1 for 20 years.

2 There are still failure modes out there  
3 today. As I said there is a pacemaker manufacturer  
4 who had a hermetic sealing problem with leakage in  
5 recent years. Within the last five to seven years.

6 I am not saying that we are the only ones  
7 who can do it. There are other people who can do  
8 this, other quality manufacturers out there making  
9 pacemakers, for example.

10 What I am saying is it is real darn hard,  
11 as they say in the TV ads, don't do this at home.

12 I urge you, unless you find a way to  
13 replace the current system, not to move an active  
14 implantable into class II.

15 CHAIRPERSON CANADY: Dr. , do you have any  
16 additional comments to make?

17 DR. BOWSHER: No.

18 Okay, go ahead Dr. Edmondson.

19 DR. EDMONDSON: Just another question to  
20 the FDA itself.

21 I think a little bit of history could be  
22 used as a foundation before we move to vote on this.

23 Why was the implantable device was placed  
24 in class III in the first place, in the Eighties?  
25 Even though we have more clinical data over the last

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1 15 years, vis a vis the special controls that are  
2 currently in existence, really how is that improved  
3 compared to 1984?

4 CHAIRPERSON CANADY: Mr. Dillard?

5 MR. DILLARD: Could I ask for just a  
6 moment while I confer with a colleague?

7 CHAIRPERSON CANADY: If we could have the  
8 forms passed forward?

9 (PAUSE)

10 MR. DILLARD: Okay. I'm back.

11 Dr. Edmondson, could you maybe take one  
12 more shot at it? I think I have your answer, but I  
13 want to be sure to hit it right on the head.

14 DR. EDMONDSON: Whenever it was, I guess  
15 1981, when the first application was made for a  
16 totally implantable device under class II 5.10 K, it  
17 was suggested that it be processed under PMA.

18 Now, over the last 15 years or more there  
19 is a growing body of evidence regarding, we have a  
20 larger denominator to deal with in terms of what the  
21 risks are for this particular device.

22 But we are not dealing with a large number  
23 of competitive manufacturers, and that is part of the  
24 problem.

25 Now, over this time, what sort of special

1 controls, how does that work in the whole FDA  
2 mechanism here? What is the big difference between  
3 the past and present.

4 MR. DILLARD: Let me try to balance a  
5 discussion or a description about the past and  
6 present, and try not to be too leading.

7 I certainly don't want to do that in the  
8 circumstances, but I want to give you some information  
9 so that you can deliberate.

10 You have heard about pre-amendments, post-  
11 amendments, class III devices, from the training and  
12 everything else.

13 What I can say is that, from the  
14 standpoint of what the advisory committees back in the  
15 late Seventies and early Eighties were the known  
16 products on the market at the time, in order to give  
17 a classification recommendation.

18 At that time, what was on the market were  
19 the RF-coupled kinds of devices.

20 There was not an active, implantable pulse  
21 generator for this indication for use on the market,  
22 prior to May 28, 1976.

23 So, when one came in after the original  
24 classification went through, and the manufacturers  
25 claimed equivalence to the best predicate devices they

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1 could, which were the RF-coupled devices. Same  
2 indication for use, but different technological  
3 characteristics.

4 The way we analyze through 5.10 K whether  
5 something is substantially equivalent or not  
6 substantially equivalent, there are three reasons why  
7 something is not substantially equivalent.

8 Either it has a new intended use, it has  
9 different technological characteristics that raise  
10 different questions of safety and effectiveness, or  
11 data, when you compare it to a device on the market  
12 demonstrates that they do not perform equivalently.

13 I would venture a guess, even though I  
14 don't have the letter in front of me, that the reason  
15 we found the active implantables not equivalent to the  
16 RF-coupled devices was, at the time, we did believed  
17 the technological change of having the battery self-  
18 contained and the generator implanted in the body  
19 raised different questions of safety and effectiveness  
20 as compared to the RF-coupled.

21 Questions as simple as all the ones you  
22 are discussing.

23 Infection differences, we didn't have a  
24 can that was being implanted in that kind of  
25 situation.

1 Controllability, battery leakage, battery  
2 drain, all the issues that have been discussed here  
3 today, were new then.

4 So, our regulatory decision was based on  
5 the newness and the new types of questions at the  
6 time.

7 Congress envisioned, even when they gave  
8 us the medical device amendments back in 1976, a  
9 process of reclassification as more and more knowledge  
10 became available on products.

11 Now, that doesn't only pertain to  
12 reclassification from III to II, but also  
13 reclassification from II to I, II to exempt, II to I  
14 to exempt. All those permutations are possible.

15 So, the whole legal thought process was  
16 that as we gained more experience and different ways  
17 to look at risks and control for risks, that  
18 reclassification was an option for a manufacturer or  
19 manufacturers to move products to the most appropriate  
20 class based on knowledge and our ability to control  
21 risks for the product.

22 So, what has changed over 15 years, which  
23 I think is really your question? You, today, will  
24 have to judge this and we at FDA will have to judge it  
25 when we try to make a final determination on the

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1 petition.

2 Do we know something about the risks, can  
3 we characterize the risks, is there data that supports  
4 what those are and what we can say about them, which  
5 is really the statutory standard that we have to look  
6 at, and then can we control for those risks with  
7 either special controls that we have available to us  
8 or special controls that can be proposed that need to  
9 be developed prior to moving forward on  
10 reclassification.

11 That is all envisioned under the scope of  
12 the legislative environment and our regulations for  
13 reclassification.

14 So, 15 years has changed things. There is  
15 more data that we have to look at, I am not saying it  
16 supports reclassification or not, there is different  
17 kinds of testing procedures, there are different  
18 regulatory authorities that we can apply for control  
19 or risks.

20 Whether or not it is enough is what is  
21 going to be difficult by today's standards.

22 But the reason we are where we are today  
23 is because technology, knowledge base, and clinical  
24 information have changed, and that, at any point in  
25 time, can be used to take a look at what the most

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1 appropriate class is.

2 So, it isn't anything magical. It is just  
3 a matter of time and knowledge base in both the pre-  
4 clinical and clinical arena that can really be the  
5 force behind reclassification.

6 DR. EDMONDSON: Now with regard to special  
7 pre-market controls, clinical research before  
8 marketing under class II versus PMA how does that  
9 work.

10 MR. DILLARD: Well, let me give a general  
11 answer. Maybe I gave this earlier in one of the other  
12 sessions.

13 We do have the ability as an agency, as  
14 FDA to ask for clinical data for class II 5.10 K  
15 products.

16 The issue would be, and would tend to be  
17 an issue-based organization, that we try to look at  
18 the right amount of data to answer whatever the issues  
19 are associated with the product.

20 So, of you looked at it as a bottom-up  
21 kind of situation, many times we will look at it and  
22 say there is a certain level of issues we have to  
23 answer.

24 If pre-clinical information can answer  
25 those issues, then that would be enough to make a

1 decision of substantial equivalence.

2 We wouldn't just inappropriately or  
3 halfheartedly ask for an animal study, for instance or  
4 a clinical study.

5 We should be asking for data that answers  
6 an issue, and then we need the right kind of study to  
7 answer the issue.

8 Pre-clinical or animal or clinical data  
9 may be appropriate under those circumstances.

10 So, that option is available to us under  
11 5.10 K and may be necessary under circumstances where  
12 there may be product modifications or new products  
13 that are trying to get on the market.

14 There is a lot I could say but I am going  
15 to try to say enough to give you a clearer picture  
16 about the difference between class III and class II  
17 and clinical data because that is a very sticky point  
18 and a very tough issue.

19 If you are going to base purely on  
20 clinical data, when is clinical data for class II any  
21 different from clinical data for class III and where  
22 do you draw that line? And that is not cast in stone.

23 One of the tests that I think has been  
24 used for classification and reclassification is if the  
25 kind of clinical information that would be needed for

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1 a next of a kind device would be clinical data that,  
2 where there is a well-established knowledge base of  
3 clinically what happens in the safety and  
4 effectiveness arena, and what you were doing was  
5 getting clinical data to show that it was equivalent.

6 Also, if there weren't any new issues, it  
7 didn't necessarily have to be something that  
8 absolutely demonstrated safety and effectiveness,  
9 because that is the different standard for a PMA  
10 device versus equivalence for a 5.10 K device, versus  
11 whether or not you really believe each individual  
12 device has to have its own clinical data set that  
13 prospectively is defined so that you can a priori say  
14 it is a safe and effective device before it is on the  
15 market, that is kind of the class III standard.

16 So, if you believe there has to be that  
17 level of clinical data then perhaps what you may be  
18 saying that it still needs to be a class III device.

19 More towards a class II recommendation,  
20 using equivalent data, there is a good body of  
21 knowledge and you just need to show that you fit  
22 within a well-known and well-defined scheme of  
23 clinical performance.

24 I hope that has helped and not confused.

25 CHAIRPERSON CANADY: Other questions or

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1        comments?

2                    We can begin with the forum then.

3                    We will do this similarly to the last  
4        time.    The first three questions we will do as a  
5        straight vote.    I think there will be some comments as  
6        we get farther on and we will invite some  
7        conversation.

8                    The first one is, "Is this device life-  
9        threatening or life-supporting?"

10                   Again the industry and consumer reps don't  
11        vote.    I've learned something.

12                   All who would say YES, please raise your  
13        hands.

14                   If you would say NO, please raise your  
15        hands.

16                   Six NOs.

17                   "Is the device for a use which is of  
18        substantial importance in preventing impairment of  
19        human health?"

20                   All who would say YES, please raise your  
21        hands.

22                   All who would say NO, please raise your  
23        hands.

24                   I have three votes on one side.    Gentlemen  
25        are you abstaining?

1 DR. GONZALES: I am actually still  
2 thinking about a YES vote.

3 CHAIRPERSON CANADY: That's fine.

4 DR. GONZALES: You are asking for NOs,  
5 right now correct?

6 CHAIRPERSON CANADY: Is everybody ready to  
7 vote, let me start with that?

8 DR. GONZALES: I am ready.

9 CHAIRPERSON CANADY: Second question, "Is  
10 the device for a use which is of substantial  
11 importance in preventing impairment of human health?"—

12 All who would say YES, please raise your  
13 hands.

14 Three YES votes.

15 All who would say NO, please raise your  
16 hands.

17 Three NO votes.

18 CHAIRPERSON CANADY: I am going to vote no  
19 as the tie-breaker.

20 Number three, "Does the device present a  
21 potential unreasonable risk of illness or injury?"

22 Are we ready for a vote or more thought?

23 I didn't write the questions.

24 All who would say YES, please raise your  
25 hands.

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1 All who would say NO, please raise your  
2 hands.

3 Five NOs, one abstained.

4 Number four is obvious, we said as a  
5 group, no, to all of the questions above.

6 I note again, individually you complete  
7 your form as you see fit. It is important you don't  
8 have to follow the group on your own form.

9 That takes us to item number five,  
10 correct?

11 MS. SHULMAN: Correct.

12 CHAIRPERSON CANADY: "Is there sufficient  
13 information to determine that general controls are  
14 sufficient to provide reasonable assurance of safety  
15 and effectiveness?"

16 All who would say YES, please raise your  
17 hands.

18 All who would say NO, please raise your  
19 hands.

20 Six NOs.

21 Number six, "Is there sufficient  
22 information to establish special controls to provide  
23 reasonable assurance of safety and effectiveness?"

24 All who would say YES, please raise your  
25 hands.

1 That is five.

2 All who would say NO, please raise your  
3 hands.

4 Five YES, one abstention.

5 DR. GATSONIS: The form is a little  
6 confusing. It says if you said YES to any of the  
7 first three then you have to go to item seven. So,  
8 you don't answer five or six.

9 MS. SHULMAN: Correct. But we didn't say  
10 yes to any of the first three.

11 DR. GATSONIS: But if somebody did.

12 CHAIRPERSON CANADY: Now, we get to number  
13 seven which is a delineation of what we think those  
14 special controls should be.

15 Let's do it in a similar manner to how we  
16 did last time; I will go by the grouping they have,  
17 and then I will open conversation for any additional  
18 points.

19 Post market surveillance?

20 All in favor?

21 MS. SHULMAN: You didn't answer YES or NO.

22 CHAIRPERSON CANADY: He doesn't have to.

23 I am not going to put him on the spot again.

24 All in favor of performance standards?

25 DR. KU: I have a question.

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1 CHAIRPERSON CANADY: Yes?

2 DR. KU: With performance standards, can  
3 you specify rates of failure of the device?

4 MS. SHULMAN: You certainly can.  
5 Performance standards are the ones recognized by rule  
6 making.

7 By rulemaking through the FDA.

8 DR. KU: So you could say that current  
9 failure rate is three per cent, we want to be sure you  
10 guys meet three per cent or better?

11 MR. DILLARD: I just want to clarify.

12 This is a point that everybody gets stuck  
13 on every time we do this forum.

14 You have probably never seen a performance  
15 standard. One we have been working on for 15 years  
16 and I believe went final was on apnea monitors.

17 One you may have seen was on cable leads,  
18 male and female. It was based on a number of reported  
19 deaths of plugging a male lead into a wall socket;  
20 being able to do that.

21 That is an FDA-mandated performance  
22 standard that all manufacturers of a kind of product  
23 have to adhere to.

24 We have to go out with a proposed rule,  
25 get comments then go final, just like we would in any

1 rule-making like a classification process.

2 That is specifically what we are talking  
3 about here for performance standards.

4 Any other kind of standard, an industry  
5 standard, either consensus or non-consensus, and  
6 international standard, you would want to put under  
7 "Other" in terms of standards.

8 So, if you believe we need to promulgate  
9 an FDA-based performance standard for these products,  
10 that is where you would mark YES on this one.

11 CHAIRPERSON CANADY: Any other questions—  
12 for clarifications?

13 DR. GONZALES: So, since the issue is the  
14 battery and battery function, and problems with the  
15 battery, the implantable, would that be under  
16 performance standard, to look at that subtype very  
17 specifically and in detail?

18 Or would that be under "Other"?

19 MR. DILLARD: It could be either one. I  
20 know that is not the answer you are looking for.

21 The fact of the matter is that if you are  
22 concerned about a specific component of a device, but  
23 you believe there is already existing industry  
24 standard, for example, that has been referenced, that  
25 covers battery life, that you believe is imperative

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1 for any manufacturer of kind of this product to meet  
2 that standard, but it is a consensus standard, an AMI  
3 standard or an ANSI standard, that would go under  
4 "Other".

5 If you think we need to take not only that  
6 knowledge and FDA knowledge and other general  
7 knowledge about batteries and actually promulgate  
8 a performance standard that would be a regulatory  
9 standard, then you would check performance standard  
10 here.

11 DR. GONZALES: Then could I ask Dr. Walker-  
12 to comment on whether there is a standard for battery  
13 failure? Not just failure in terms of loss of power,  
14 but other aspects of failure such as leakage,  
15 toxicity.

16 Are there such standards?

17 DR. WALKER: I am not aware of any  
18 voluntary trade or non-proprietary standards?

19 Medtronic may have a standard they use  
20 internally, but that is not what we are talking about  
21 here.

22 DR. GONZALES: So, then I believe battery  
23 function as far as abnormalities would be under  
24 "Other" since there is no standard performance.

25 CHAIRPERSON CANADY: Are we ready to vote

1 on the issue of performance standards now?

2 All who would say YES, please raise your  
3 hands.

4 All who would say NO, please raise your  
5 hands.

6 Six NOs.

7 Patient Registries?

8 All who would say YES, please raise your  
9 hands.

10 All who would say NOs, please raise your  
11 hands.

12 All confused?

13 Is there confusion on this?

14 Can we clarify that category?

15 DR. WITTEN: I mean you want clarification  
16 on what is a registry?

17 CHAIRPERSON CANADY: That's correct.

18 DR. WITTEN: It is a record of the  
19 patients who have received the product.

20 But I don't think it means that we  
21 actively get information about what has happened.

22 MR. DILLARD: Jim Dillard.

23 From the standpoint of registry here, many  
24 manufacturers, and this is different in post-market  
25 surveillance because surveillance would be something

1 that they would actively be doing, but a registry here  
2 would serve more as something that a manufacturer  
3 would try to get as much information on a patient.

4 They might do it by a post card, a record  
5 of what they are doing, keeping an ongoing log of the  
6 types of patients and a small amount of data that is  
7 going on.

8 But to be able to have some information  
9 but not necessarily to the extent that post-market  
10 surveillance is looking for something specifically  
11 that may need to be clarified later on with data.

12 MS. WOJNER: Clarification.

13 So, in other words you can do post-market  
14 surveillance without a patient registry, but it  
15 doesn't work the other way.

16 You need to have some form of a registry  
17 in place to do post-market surveillance. But the  
18 registry itself is not enough to give you the degree  
19 of data necessary to support?

20 MR. DILLARD: I almost think of it as a  
21 hierarchy and hopefully this doesn't bias anybody.

22 I think of a post-approval study, for  
23 example, as being the highest form of post-approval  
24 requirements.

25 You actually have to go do something that

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1 is prospective, post-market study to either gather  
2 some information or answer some questions. It would  
3 be intended to gather some data to support an issue  
4 that perhaps came up in the approveability of a device,  
5 for example.

6 Surveillance would be more on the end of  
7 looking for trends of something that might have been  
8 a low-level adverse event.

9 You aren't really trying to answer it,  
10 just trying to get a broad data base to give you a  
11 sense of whether or not it is different than your pre-  
12 market study, for example.

13 But it would be something where you were  
14 looking for some data but not necessarily from a real  
15 prospective, post-approval type of study.

16 Then I would go one step further to a  
17 patient registry would not be focused on data or a  
18 specific issue, but nonetheless, some information that  
19 the manufacturer could use in the future to support a  
20 multitude of things.

21 This could be used for other kinds of  
22 claims, to further clarify rates they may have put in  
23 their labeling when it was approved or reclassified,  
24 legal purposes.

25 I think there is a multitude of reasons.

1 CHAIRPERSON CANADY: Dr. Ku?

2 DR. KU: Can I ask one more clarifier in  
3 relation to that?

4 Who decides which data are collected in  
5 that post-market surveillance category?

6 MR. DILLARD: If you recommended, and we,  
7 in a reclassification effort or an approval of a  
8 product, thought that post-market surveillance was  
9 necessary.

10 You heard some in training about what some  
11 of our authorities are in post-market surveillance.  
12 There is no longer any required post-market  
13 surveillance based on FDA as of May, 1997.

14 It is all discretionary post-market  
15 surveillance.

16 So, it would be a discussion between us  
17 and the manufacturer to come to an agreement on post-  
18 market surveillance effort and what kind data.

19 CHAIRPERSON CANADY: Dr. Ku?

20 DR. KU: So, the long and short of it is  
21 if we are recommending post-market surveillance, by  
22 default there is a registry.

23 MR. DILLARD: I can't definitively say  
24 that.

25 But I can say in general, that would be a

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1 higher order of the level of post-market activity that  
2 would be needed.

3 CHAIRPERSON CANADY: Other questions?

4 Are we ready to vote on that issue?

5 "Patient Registries."

6 All in favor say YES.

7 NO?

8 Four positives

9 "Device tracking."

10 All in favor say YES.

11 DR. WALKER: Can I get a point clarified?

12 CHAIRPERSON CANADY: Sure.

13 DR. WALKER: I thought we decided we were  
14 going to track which device goes into which patient.

15 CHAIRPERSON CANADY: We are; that is the  
16 default.

17 DR. WALKER: That is the patient registry?

18 CHAIRPERSON CANADY: That is going to be  
19 our recommendation, yes.

20 DR. WALKER: Then what is device tracking?

21 MS. SHULMAN: Just the device versus the  
22 patient. Where is the device and where is the  
23 patient. Sometimes they aren't in the same place.

24 Not necessarily with this device, but for  
25 this form.

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1 DR. WITTEN: Can I just clarify? As Mr.  
2 Dillard just said it is a hierarchy and device  
3 tracking is just knowing where the device is, usually  
4 with the patient, but not actually gathering any  
5 information.

6 If there was a problem with the device and  
7 you needed to contact the patients because of some  
8 safety concern.

9 CHAIRPERSON CANADY: Questions clarified?  
10 Shall we vote on this issue, "device  
11 tracking"?

12 All in favor say YES.

13 It is five positives.

14 All in favor say NO.

15 "Testing guidelines".

16 All in favor say YES.

17 Clarification for "testing guidelines"?

18 MR. DILLARD: Jim Dillard.

19 There is not a huge distinction here  
20 between testing guidelines and guidance documents and  
21 other standards that you would recommend.

22 I think if there were a known guideline or  
23 even a guidance document, we use guideline and  
24 guidance fairly interchangeably, as opposed to a  
25 standard which brings with it a little bit different

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1 connotation.

2 So, if there is a known guideline that you  
3 know of, and it may not be an FDA-promulgated  
4 guideline, but it might be a professional society  
5 guideline, you might check it and reference what it  
6 is.

7 So, it is a very non-descript way to  
8 attack the guidance issue.

9 CHAIRPERSON CANADY: Other questions?  
10 All in favor of "testing guidelines"?  
11 All opposed?

12 I have two and two; I am going to say NO.  
13 So, three and two.

14 MS. WOJNER: Could the panel specify under  
15 the "Other" category, specific post-market  
16 surveillance data that we would feel worth of  
17 collection in a CQI or whatever process?

18 CHAIRPERSON CANADY: I don't see why not.  
19 The floor is now open to such  
20 recommendations regarding anything additional you  
21 would like to see added to the special controls.

22 DR. GONZALES: Since we voted against  
23 performance standards because they don't exist  
24 regarding battery function, and that was the crux of  
25 the potential problem or difference, a standard or

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1 some set of follow-up for battery or battery function  
2 needs to be discussed and a direction given to the  
3 company.

4 I think that the person who is the expert  
5 is Dr. Walker, so I would put it in his lap to help us  
6 with that kind of standard development.

7 DR. WALKER: Well, let me see what I can  
8 do.

9 There exists a standard that says how  
10 these devices should be tested and what kind of load  
11 they should be tested on and what are the maximum and  
12 minimum rates.

13 Perhaps we might, by reference, want to  
14 incorporate that standard for output and byphasic and  
15 ODC and that sort of thing.

16 I think that is a good standard because I  
17 was on the committee that wrote it, along with Dr.  
18 North.

19 With respect to battery output, certainly  
20 one option would be to impose on this indication for  
21 a class II device the same sorts of annual reports,  
22 bi-annual inspection and pre-market visits that are  
23 imposed on class III implantable devices.

24 My recommendation would be to adopt what  
25 is already being done with other class III implantable

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1       simulators, rather than trying dream up our own as we  
2       sit here on a Friday afternoon.

3               CHAIRPERSON CANADY: So are we saying then  
4       that the standard that we want is the same post-market  
5       standard as a class III but not the same pre-market  
6       standard?

7               DR. WALKER: Correct, because the class  
8       III requires clinical trials.

9               CHAIRPERSON CANADY: Is that a reasonable  
10      thing form the FDA's perspective?

11              MS. MAHER: Well, can I say something?

12              The annual report aspect is actually a  
13      requirement of the PMA procedure and how you handle  
14      the PMA section of the law. It is not part of the  
15      substantial equivalent section.

16              So, I think what you are actually asking  
17      for needs to defined more clearly here, such as some  
18      sort of annual report on the performance of the  
19      device, not an annual report as defined under the PMA  
20      sections.

21              I am not quite sure what you are looking  
22      for, but I don't think you are looking at a PMA-type  
23      annual report.

24              CHAIRPERSON CANADY: I'm looking for an  
25      annual report on battery-related complications.

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1 DR. WALKER: Sure. Device failures.

2 DR. EDMONDSON: I think, too, before the  
3 special control pre-market should include a limited  
4 clinical study to look at the hardware performance  
5 with regard to any inopportune stimulation, battery  
6 function in situ.

7 CHAIRPERSON CANADY: Dr. Ku?

8 DR. KU: I am not convinced that the  
9 clinical study is needed.

10 You can bench-top test this thing and  
11 achieved a reliability of .03 per cent failure rate--  
12 for 100 different devices, then implanting it, the  
13 technology is known.

14 CHAIRPERSON CANADY: Well, let's put the  
15 two recommendations for "Other" to a vote.

16 One would be "that there would be an  
17 annual report regarding device failures".

18 All in favor?

19 That is six.

20 Opposed?

21 "That there would be a clinical study  
22 regarding hardware performance."

23 All in favor?

24 DR. EDMONDSON: Can I make a comment?

25 CHAIRPERSON CANADY: Sure.

1 DR. EDMONDSON: Again, before the motion.

2 I would like to make another push for a  
3 clinical study before release.

4 There are many nuances that you can test  
5 in the laboratory to determine frequency, output, all  
6 of these engineering issues.

7 But when you implant a device and somebody  
8 goes out and mows their lawn and a number of other  
9 things, there may be some nuances intrinsic to that  
10 device. So I think that a limited study that focuses  
11 questions is really warranted.

12 CHAIRPERSON CANADY: Okay we will put that  
13 question to a vote a second time.

14 All in favor raise your hand.

15 All opposed.

16 Four to two, opposed.

17 MS. WOJNER: Dr. Canady, I just want to  
18 let the record state that I think that Dr. Gonzales  
19 has brought up some very important points about a 25  
20 per cent "Other" section and I would hope that FDA and  
21 the manufacturing sector would do something logically  
22 about coming up with some very clear descriptors other  
23 than a broad-based "Other" section so that we are  
24 absolutely certain of what is occurring.

25 CHAIRPERSON CANADY: Other comments.

1 Dr. Gonzales?

2 DR. GONZALES: I have changed my vote  
3 because now that we have included reports on  
4 performance, complications, failures and inspections  
5 up to class III standards, I am satisfied that the  
6 change of the classification from III to II, now that  
7 I know we are able to impose those kinds of follow-  
8 ups, restrictions, and inspections. Up to this point  
9 I was not aware that we would be able to do that.

10 CHAIRPERSON CANADY: I'm not sure we have  
11 done that.

12 DR. GONZALES: We may do that.

13 CHAIRPERSON CANADY: We have recommended  
14 that there be an annual report of device failures.  
15 That is the only additional standard other than the  
16 ones that we have voted on and added.

17 If there are additional things that we  
18 wish to add, such as inspections, then we need to say  
19 that.

20 Dr. Walker?

21 DR. WALKER: I had put up some suggested  
22 changes to the labeling. Would this be an appropriate  
23 time to add those to our laundry list?

24 CHAIRPERSON CANADY: I would be. Does  
25 everyone recall them or do we need to see them again?

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1 The issues of language.

2 Can we vote that we recommend those  
3 changes?

4 All in favor raise your hand.

5 All opposed?

6 I believe that completes number seven.

7 DR. GONZALES: Can I make a recommendation  
8 as Dr. Walker stated earlier, that inspections to the  
9 class III standards be imposed?

10 CHAIRPERSON CANADY: Yes. And I would ask  
11 that we vote on that.

12 All in favor raise your hand.

13 Opposed?

14 That is six YES.

15 MS. MAHER: Before we move on, could I ask  
16 Jim Dillard how that would be moved forward, in  
17 interaction with the compliance and evaluation group?

18 MR. DILLARD: Jim Dillard.

19 In terms of that recommendation up to  
20 class III standards of inspection, I think I can tell  
21 you how we would interpret that recommendation which  
22 is what I think Sally is getting at.

23 The interpretation of that in my mind  
24 would be that we put this in the higher category to do  
25 what we should be doing by regulation.

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1 That is inspect every couple of years, do  
2 a full inspection.

3 Certainly, in this particular product line  
4 for a manufacturer because the fact of the matter is  
5 when we go in and do an inspection at a manufacturing  
6 facility and the manufacturer may have multiple lines  
7 of products, we don't inspect every line and every  
8 procedure.

9 We go in and take some statistical  
10 samplings and look at various aspects of a process and  
11 see whether or not, in general, they are in compliance  
12 with the quality system regulation.

13 I think the interpretation that I would  
14 take away from this is that you are saying is what we  
15 should do is inspect every two years not every five  
16 years because it is one of those devices that should  
17 have a kick-up factor.

18 Number two, it ought to be a target of  
19 every inspection that we have at that facility, to  
20 make sure that we inspect this particular product and  
21 product line every time, in addition to others.

22 But from the standpoint of a pre-clearance  
23 inspection which a class III PMA product would have,  
24 that generally would not be something that we would do  
25 nor would we make that a high priority.

1 But, the fact of the matter is that yes,  
2 you are making a recommendation. I agree with Dr.  
3 Canady on that.

4 The other thing is your discussion on this  
5 and having a strong position helps us then to focus on  
6 these issues when we are making our final regulatory  
7 action.

8 So, keep that in mind.

9 DR. KU: Can we make pre-market inspection  
10 part of this recommendation?

11 The reason is that I think we are breaking -  
12 new ground and there may be something that may be  
13 warranted.

14 This obviously can be re-reviewed for  
15 reclassification in five years, whatever.

16 MR. DILLARD: Dr. Canady, would you like  
17 me to comment on that again?

18 CHAIRPERSON CANADY: I guess I want to  
19 comment on that.

20 I am not sure that accomplishes what we  
21 want, as I think about it.

22 The real issue is whether there is going  
23 to be battery failure.

24 I am not sure that can be addressed  
25 directly at the pre-market inspection.

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1 DR. KU: but don't they need to evaluate  
2 the entire manufacturing process at that time?

3 Or is that already done?

4 CHAIRPERSON CANADY: I think that would be  
5 part of the normal process, as part of the discussion.

6 Mr. Dillard?

7 MR. DILLARD: The inspection, whether it  
8 is a class III or a class II, if we are inspecting the  
9 product line we look at the processes that the  
10 manufacturer has, at the specifications, if they have  
11 tested in accordance with the specifications and have  
12 recorded the data in a log.

13 That isn't too different between a class  
14 III and a class II device.

15 You look for the same veracity in the  
16 data, their adherence to their own internal processes,  
17 that they have to do the specific things that you are  
18 talking about in terms of battery testing, overall  
19 product testing, hermetic sealing and everything else.

20 CHAIRPERSON CANADY: Ms. Wojner?

21 MS. WOJNER: I was just going to say that  
22 my advice to the committee that if we are going to add  
23 much more to the list are we really making the right  
24 decision to say that this is a class II.

25 I am not sure we have to go so far as a

1 pre-market inspection.

2 The task before us is that if we are going  
3 to go with a class II that we insuring a certain  
4 degree of quality and standardization.

5 I think that what is on the list  
6 accomplishes that.

7 CHAIRPERSON CANADY: Other comments?

8 Then I would like to vote on that issue of  
9 whether we wish to include a pre-market inspection.

10 DR. KU: I withdraw it.

11 CHAIRPERSON CANADY: You withdraw it?

12 Then I would like to go over question  
13 seven as it is not constituted which would be to have  
14 post-market surveillance, patient registries, device  
15 tracking, inspection at level III and device failure  
16 reporting on an annual basis.

17 In essence, do you agree to the package?

18 All in favor raise your hand.

19 Opposed?

20 That is five YES to one NO.

21 DR. WITTEN: Can I ask for some  
22 clarification?

23 You haven't commented anywhere on those  
24 things that the sponsor suggested as special controls.

25 Were you meaning to include some or all of

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1 the controls, they suggested, the sponsor of the  
2 reclassification petition.

3 The other thing I wasn't sure if you were  
4 voting on the list? or is there sufficient information  
5 to establish special controls.

6 CHAIRPERSON CANADY: We were voting on the  
7 overall package.

8 The first part of question seven is there  
9 sufficient information establish special controls.

10 MS. SHULMAN: Okay, then I guess it is  
11 just a matter of housekeeping to make sure that nobody  
12 is confused.

13 If you just want to vote, I know it is a  
14 repeat of question six, but just yes or no to classify  
15 it as class II.

16 CHAIRPERSON CANADY: All in favor of  
17 special controls?

18 Opposed?

19 Five YES, one NO.

20 Now, do we want to address the special  
21 controls as presented by ANS?

22 Dr. Walker?

23 DR. WALKER: Let me suggest that we adopt  
24 them. I have suggested some changes to them and lets  
25 adopt them.

1 CHAIRPERSON CANADY: All in favor of that  
2 approach say AYE.

3 Opposed?

4 Six to zero.

5 I believe that may complete question  
6 seven.

7 Number eight is a regulatory performance  
8 standard is required to provide reasonable assurance  
9 of the safety and effectiveness of a class II or III  
10 device.

11 MS. SHULMAN: You can skip question eight  
12 and we can skip nine because that goes with question  
13 eight. We can skip question ten because that is for  
14 PMAs.

15 CHAIRPERSON CANADY: Okay. We are back to  
16 number 11, "Can there otherwise be reasonable  
17 assurance of its safety and effectiveness without  
18 restrictions on its sale, distribution or use of any  
19 potentiality for harmful effects or the collateral  
20 measures necessary for the device's use.

21 MS. SHULMAN: Please remember that voting  
22 no makes it a prescription device.

23 CHAIRPERSON CANADY: All in favor raise  
24 your hand.

25 Opposed?

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1 Six NOs.

2 The first one is "Only upon the oral or  
3 written authorization of a practitioner, licensed by  
4 law to administer or use the device."

5 Yes?

6 No?

7 The next one would be, "Only for use by  
8 persons with specific training or experience in its  
9 use."

10 Yes?

11 MS. WOJNER: Point of clarification on  
12 that.

13 Does that second category encompass  
14 technicians who are involved in programming these  
15 devices once they have been implanted?

16 CHAIRPERSON CANADY: That you would have  
17 to make as a recommendation.

18 She is presuming that the programming may  
19 not be done by physicians.

20 MS. SHULMAN: Usually it is not.

21 CHAIRPERSON CANADY: That is what I am  
22 saying. So should there be special training?

23 MS. WOJNER: Are you waiting for an  
24 answer?

25 CHAIRPERSON CANADY: I guess my view is

1 that it would be done under the direction of a  
2 physician and that the training should be so specified  
3 in that context.

4 MS. WOJNER: Okay. Would that include a  
5 licensed nurse practitioner or a clinical nurse  
6 specialist, for instance.

7 CHAIRPERSON CANADY: I would say they are  
8 not independent. But that is my personal view.

9 Are you ready to vote on this issue?

10 "Use only by persons with specific  
11 training or experience in its use."

12 Yes?

13 Three YES.

14 No?

15 Three NO. I am going to say NO, as a tie  
16 breaker.

17 "Use only in certain facilities."

18 Yes?

19 No?

20 Six.

21 Any other restrictions the panel would  
22 feel need to be applied or would like to apply?

23 I believe we have completed this form.

24 MS. SHULMAN: All right, now we have the  
25 second one.

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1 CHAIRPERSON CANADY: Do we have to vote on  
2 the form?

3 MS. SHULMAN: You may vote on both of them  
4 together.

5 CHAIRPERSON CANADY: Under question four,  
6 indications for use, I would suggest that we are not  
7 proposing any changes in the indications.

8 MS. SHULMAN: So, we can put on there, as  
9 in the reclassification petition?

10 CHAIRPERSON CANADY: Right.

11 "Identification of any risks to health-  
12 presented by device."

13 Comments?

14 Recommended advisory panel classification,  
15 class II.

16 Do we still need to put a priority on this  
17 one, Dr. Witten?

18 DR. WITTEN: Yes, they need high, medium  
19 or low.

20 CHAIRPERSON CANADY: High, medium or low  
21 priority.

22 Any comments?

23 All in favor of high, raise your hand.

24 Medium?

25 Low?

1 "If the device is an implant or is life-  
2 sustaining or life-supporting, and has been classified  
3 in a category other than class III, explain fully the  
4 reasons for the lower classification with supporting  
5 documentation and data.

6 The summary of information would be the  
7 presentations made here today, the petition and the  
8 written material. Any additional information people  
9 would like to include under the last category?

10 Any additional restrictions people would  
11 like to place?

12 Any comments or questions before we vote  
13 on these documents?

14 MS. SHULMAN: There is one more question.

15 On the back of that you can skip question  
16 ten because that is for class I device.

17 Question eleven, "existing standards to  
18 the device, components or device materials parts or  
19 accessories".

20 CHAIRPERSON CANADY: Any comments or  
21 questions?

22 Hearing none, we will vote now on  
23 accepting the documents together as completed by the  
24 group.

25 All in favor, raise your hand.

1 All opposed?

2 It is 5 for and 1 against.

3 Other business?

4 The next meeting of this panel will be  
5 December 10, 1999.

6 Otherwise, we will now adjourn.

7 DR. WITTEN: I'd like to thank the panel  
8 and the FDA and the industry people who have been here  
9 today for your help.

10 (Whereupon, the proceedings recessed at  
11 3:29 p.m.)

CERTIFICATE

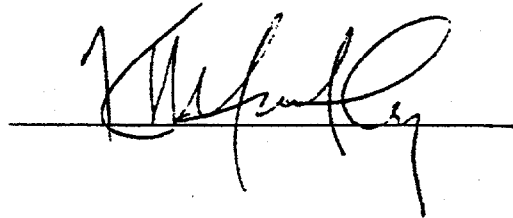
This is to certify that the foregoing transcript in the  
matter of:                   Neurological Devices Panel of the  
                                  Medical Devices Advisory Committee

Before:                   DHHS/FDA

Date:                   September 17, 1999

Place:                   Rockville, MD

represents the full and complete proceedings of the  
aforementioned matter, as reported and reduced to  
typewriting.



**Attachment C**  
**Dr. Alpert Letter**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

DEC 29 1995

Food and Drug Administration  
9200 Corporate Boulevard  
Rockville MD 20850

Mr. Robert J. Klapinski  
Senior Legal Counsel  
Medtronic, Inc.  
Law-Department  
7000 Central Avenue, NE  
Minneapolis, Minnesota 55432-3576

Re: C950010 -- Classification of Medtronic Itrel™  
Dated: November 22, 1995  
Received: December 20, 1995

Dear Mr. Klapinski:

This is response to your request to Mr. Fred Sadler for classification information dated November 22, 1995. The Medtronic Itrel™ Totally Implantable Spinal Cord System was determined by FDA to be a class III device by order dated October 29, 1980, (copy enclosed). The Food and Drug Administration (FDA) determined that the Medtronic Totally Implantable Spinal Cord System was not substantially equivalent to any device marketed prior to May 28, 1976, or to any device classified as a class I or class II device; therefore it could not be marketed until FDA approved a premarket approval application in accordance with Section 513(f) of the Federal Food, Drug, and Cosmetic Act.

As specified by Section 513(f) of the Food, Drug, and Cosmetic Act (act), a device to be marketed after May 28, 1976, is classified into class III unless the FDA determines the device to be substantially equivalent to a preamendments device, or the device is reclassified into class I or class II.

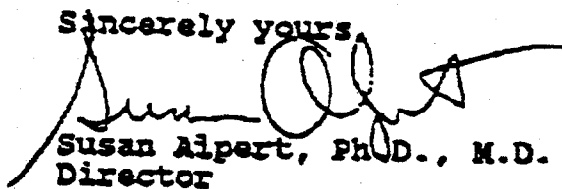
FDA determined that this Medtronic device was not substantially equivalent to devices classified in Title 21, Code of Federal Regulations, Section 882.5880 (21 CFR 882.5880) based on significant technological differences. For example, the Medtronic device employs an implanted device containing a power source; whereas, the devices classified in 21 CFR 882.5880 employs an implanted device comprised entirely of passive components with necessary energy being provided by an external device.

As further evidence of this determination, FDA sent to Medtronic, Inc. on August 2, 1989, an order approving the Premarket Approval Application (PMA) for the Medtronic Itrel II™, which includes a Model 7424 Implantable Pulse Generator and a Model 7496 Quadrapolar Extension.

Page 2 - Mr. Robert J. Klepinski

We believe this unequivocally establishes that Medtronic Totally Implantable Spinal Cord System is by statute a class III device for which an approved PMA is required for marketing. If you have further questions, please contact Robert F. Munzner, Ph.D., at (301) 443-8517.

Sincerely yours,



Susan Alpert, Ph.D., M.D.  
Director  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosure

Attachment D  
Dr. North Letter

**Department of Neurosurgery**

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Baltimore, MD 21287-7713  
410-955-2438 / FAX 410-955-9112

Richard B. North, M.D.  
Professor of Neurosurgery,  
Anesthesiology and Critical Care Medicine

Director, Functional Neurosurgery  
Director, Neurosurgery Spine Service

January 15, 2000

Office of Device Evaluation  
Center for Devices and Radiological Health  
U.S. Food and Drug Administration  
9200 Corporate Blvd.  
Rockville, MD 20850

**To Whom It May Concern:**

As a participant in the September 17, 1999, Panel proceedings concerning the reclassification of "Totally Implanted Spinal Cord Stimulator for Pain Relief," I have several observations and concerns.

First, it was apparent to me that the Panel was not well informed as to the nuances of Class III device restrictions versus Class II device restrictions. Throughout the proceedings there were numerous Panel questions raised that went unanswered or were given inappropriate responses. The questions ranged from manufacturing controls to post market surveillance. The nature of these questions indicated to me that the Panel did not have the background they needed to make a well-informed decision.

Secondly, I would point out that the Medtronic Corporation showed restraint in communicating the failures of other companies. Specifically, Medtronic had knowledge (as did I) that an acquisition of the petitioner had grossly failed a clinical trial using an implantable pulse generator – the only such trial in the petitioner's experience - and the petitioner failed to communicate any of the historical information regarding this effort to the Panel. In this instance, the safeguards of a Class III device had allowed a pre-PMA inspection by the FDA. This inspection discovered under-reporting of MDR's, lack of manufacturing compliance, and multiple adverse patient events that were not reported in the PMA application. These facts would not have been known if a pre-PMA inspection had not occurred, and the device would have been released to market for use in the general public. Medtronic used good business practice in refraining from naming the company involved and pointing out the lack of forthrightness on the petitioner's part; but the Panel apparently remained completely unaware of this unfortunate history.



The petitioner pointed out that relatively few spinal cord stimulator failures have involved the "totally implanted" pulse generator, but their data were almost entirely based upon one product line of one manufacturer (namely, Medtronic, Inc). As there are no other companies producing reliable systems, we should not draw any conclusions from this solitary and extraordinary example.

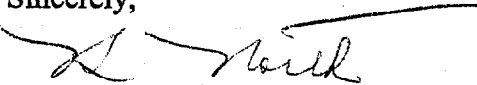
If a new product were introduced into the market under Class II, without the rigors of a Class III designation, there would be doubt about the reliability of the device. For example, battery end of life might occur without ample warning time to allow for elective/scheduled replacement of the device. An emergency situation might ensue. Other failure modes (e.g. battery leakage) might be even less forgiving. In my personal experience with the IPGs produced by the petitioner's acquisition, all failed prematurely and unexpectedly. Class III safeguards addressed the problem, while the number of cases remained small.

If more than one company were marketing reliable Class III implantable pulse generators for spinal cord stimulation, down classification might be reasonable. As this is not the case, it is not prudent to allow such a reduction in restrictions to market. This is especially true when after market release the FDA has no control over medical practice, and a physician can use a device for any indication, anatomical site, or treatment option. In my opinion this is the another significant risk the FDA is taking in the matter: granting Class II to an active implantable device that may be used in any number of ways "off label".

I cannot concur with the panel recommendation. I believe it is in the best interest of public health that you keep the implantable pulse generator for spinal cord stimulation within Class III. Anything less would allow undue risk.

Thank you for your consideration.

Sincerely,



Richard B. North, MD  
Professor of Neurosurgery,  
Anesthesiology and Critical Care Medicine  
Director, Functional Neurosurgery  
Director, Neurosurgery Spine Service